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William Thomas Councilman

UNIV. OF MICH.

William Thomas Councilman

1854-1933

On May 26th, 1933, Dr. Councilman died at his summer home in York, Maine, and although he had long been away from the Johns Hopkins University, his death is felt as a great loss to his many friends and former associates here.

William Thomas Councilman was 79 years old at the time of his death. He was born at Pikesville, Maryland, January 1st, 1854, the son of Dr. John T. and Mrs. Christiana Drummond Councilman. He graduated at St. John's College, Annapolis, and then studied medicine at the University of Maryland, where he graduated in 1878. He was Medallist at the Maryland Academy of Medicine in Baltimore in 1880, Assistant Physician at the Quarantine Station, 1878–79. He became fellow in Physiology at the Johns Hopkins University in 1880, and there came under the influence of Prof. Newell Martin until 1884. Then, upon Dr. Welch's arrival, he was appointed associate in Pathology in 1886 and later associate professor of Pathology, a position which he held until 1891. During that time he was pathologist at Bay View Hospital. There he was a most eager student and became especially interested in malaria after the discovery by Laveran of the malarial parasite. Indeed, his descriptions and drawings, sent to Dr. Welch who was then in Europe, stirred the admiration and interest of Celli and Marchiafava to whom they were shown, since aside from these early workers most of the masters of pathology were skeptical of the significance of these observations. Dr. Councilman was probably the first in America to recognize the malarial parasites, and others were slow in following him.

At the Johns Hopkins University he worked with Dr. Welch, Dr. Halsted, Nuttall, Mall and the rest of that remarkable group in the old laboratory before the hospital was opened and afterward. Dr. Welch at that time recognized him as a trained pathologist and associate in his work and not at all as a pupil or subordinate. It was then that his study of amoebic dysentery with Lafleur was completed. He lived, at least for the later years of that time, in the hospital and to the

end of his life remembered with pleasure and enthusiasm the delight of association with the little crowd that worked in the new world of that hospital.

In 1892 he was appointed Shattuck Professor of Pathology at Harvard, a post which he held until his retirement in 1922, as Emeritus Professor. There he became active as a teacher and assembled round him many associates whose names have become well-known. He worked especially on cerebrospinal meningitis, diphtheria, and smallpox.

His appointment, drawn as he was from a distant university, was an innovation at Harvard where it had been the custom to seek within the walls men to fill the various chairs. It seems that he brought to Harvard a modern attitude toward Pathology which marked a new era. It was his idea to have a central laboratory at the Harvard Medical School with control of the material at Massachusetts General and City Hospitals, but when these broke away, the Brigham Hospital was the only one left, and in this he was sorely disappointed.

He loved teaching and his students and assistants were devoted to him. His interests were in pathological anatomy and especially in the various forms of infection which he studied so minutely and with such illuminating results. In conferring an honorary degree, President Eliot said of him: "A leader in medical research, an inspiring teacher, and a man of scholarly attainments." He was the recipient of many honorary degrees, the most recent from his early alma mater, St. John's in Annapolis, conferred the year before his death.

Another great interest that filled much of his leisure time was in trees and to their study he contributed a number of publications. A close friend was Sargent, the director of the Arnold Arboretum, with whom he spent many hours of discussion.

In 1894 he married Isabella Coolidge, of Boston, and with her his happy life was spent in Boston and in the summers at their pleasant home at York in Maine. They had three daughters, Mrs. William Morgan, Mrs. Frank Wigglesworth, and Dr. Elizabeth Councilman.

In 1916 Dr. Councilman accepted an invitation from Mr. Hamilton Rice to accompany him on his yacht to the source of the Amazon. Dr. R. A. Lambert, one of his most devoted admirers, went with him and their experiences are recorded in a pamphlet published in 1918. He was delighted by the opportunity to see the great Amazon forest

and revelled in the luxuriance of the tropical vegetation. Then, in 1923, he went as visiting professor to the Union Medical College in Peiping, China, and on this trip once more his intense interest in trees and plants occupied his leisure. He searched out Mayflowers in Japan and found them quite like those in Maine, the fungus parasites of which he had studied. The cryptomerias there gave him great pleasure. In Peiping he gave the course in pathology and worked hard at this, conducting clinical pathological conferences and doing some autopsies. He was greatly interested in the Chinese, he liked them and devoted himself to an attempt to learn all he could about their history and their country. Certain places were his especial favorites, the great court of the Forbidden City and the Temple of Heaven, although he would make expeditions in his rickshaw everywhere through the city. With his wife and daughter he took a long trip up the Yangtse and elsewhere. Characteristically he had no use for missionaries and very little for the legation crowd, but enjoyed talking with any old China resident who could give him information.

In Java on the way home he was delighted with the gardens in Buitenzorg. He was always excited by the tropics and stirred to an extreme by everything he saw there.

In the last years, after his return from the East, he had felt the effects of advancing arteriosclerosis with attacks of angina pectoris. The past winter he spent in Florida where he was fairly well, but he had no more than reached his summer home when the end came painlessly in one of these attacks.

The photograph, taken several years ago, shows him a rather stoutly built man, nearly bald, with an expression that fairly reveals his character. He stammered a little, couldn't spell, and in the enthusiasm that seized him upon a new idea his face grew purple. He was a most generous and liberal soul and everyone must at once share his enthusiasm and love him. Particularly with young people was he beloved, perhaps because of his liberal spirit and because he grew impatient with the conservatism of the older ones. His devotion to his teacher and friend Dr. Welch knew no bounds and his last letter was to enquire as to his well-being.

It was a life well spent and with all fulfilled that could be wished. He leaves behind him a legion of friends who loved him and will miss him greatly.

W. G. MacC.

ON THE RELATION BETWEEN THROMBOPHLEBITIS OF THE INFERIOR VENA CAVA AND OCCLUSION OF THE HEPATIC VEINS (ENDOPHLEBITIS HEPATICA OBLITERANS)

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Submitted for publication June 10, 1933

Only a few cases of obstruction to the hepatic veins have been reported in association with thrombophlebitis of the hepatic portion of the inferior vena cava. The relationship between these two pathological processes has always been a problem. A recent clinical and pathological study of a case in which this combination of lesions existed has presented us with an opportunity to study the pathogenesis of the so-called "Endophlebitis Hepatica Obliterans."

Although extensive thrombophlebitis of the inferior vena cava is not a rare pathological finding, the occurrence of this lesion in a restricted area has been seldom observed. Pleasant (1) in a series of 155 cases in which there were multiple thrombi in the vena cava, found 85 cases in which only the lower third of the vessel was involved; in 28 cases the lower and middle third were affected; in 31 cases the thrombi were found in the lower, middle and upper third; in 5 cases the middle third alone was the site of the lesion; in 5 cases the upper third alone was involved and in 1 case both the middle and upper third contained thrombi.

Cases of "Endophlebitis Hepatica Obliterans" in which the clinical course, and the pathological findings correspond to those in the case to be reported in this paper would appear to be infrequent. It has been thought advisable to review the literature on the subject of "Endophlebitis Hepatica Obliterans" with the purpose of finding out if such a lesion ever exists in the absence of a phlebitis of the hepatic portion of the inferior vena cava.

Budd (2), in 1846, was the first to report a case of "Inflammation

of the Hepatic Veins." Microscopic studies were not made in this case; however, in this discussion Budd said, "All the hepatic veins seemed thicker and more opaque than normal, and on examining them closely I found a thin, false membrane on their inner surface, which in the larger veins could be readily stripped off. There was a great deal of new fibrous tissue in all the portal canals of considerable size, and some in the small ones also—enough in the whole to render the liver tough but not distinctly hob-nailed or granular."

Frerichs (3), in 1861, in a paper dealing with endophlebitis hepatica obliterans made the following statement, "On tracing the hepatic veins from the posterior margin of the liver, the first thing observed was rounded plates (Plaques) upon the inner surface of the vena cava nearly the size of a lentil, and resembling the atheromatous plates seen in the arteries. . . . . The hepatic veins opening into the vena cava were altered in a remarkable manner. One of them was completely closed up by a pale-red nodule, the size of a cherry-stone; another terminated in a blind extremity; its walls were much thickened, and internally it was covered by numerous plates; a third was much constricted at its entrance into the vena cava, by the surrounding mass of connective tissue, while its inner wall was rough, partly brownish black, together with recent coagulum; the smaller branches were filled with these substances."

Chiari (4), in 1898, reported three cases in which he proposed to show that there could be a phlebitis obliterans of the great hepatic veins quite unassociated with any and all of the neighboring lesions and that this hepatic vein lesion need have nothing to do with a previous thrombosis; however, in the microscopic description of his first case, he stated that the walls of the hepatic veins, in their proximal parts, were somewhat thickened and showed an extreme inflammation which he characterized as an endophlebitis with associated periphlebitis, the latter being continuous with a comparable lesion in the adjacent segment of the vena cava.

In Chiari's second case, the ostia of the main branches of the hepatic veins were completely obliterated by an intimal proliferation which he interpreted as an obliterative endophlebitis primary in the hepatic veins. The branches of the hepatic veins entering the main trunks were not obliterated but showed an apparent thickening of their

walls. There was moderate thickening of the intima of the inferior vena cava in the area corresponding to the hepatic ostia, and also in the same area thrombi had formed.

In Chiari's third case, the proximal portion of the hepatic veins showed a thickening of the intima and a few fresh thrombi which often produced a complete obstruction to the larger branches of the hepatic veins.

Hess (5) in 1905, prepared a tabular synopsis of all cases of "Obliterating Endophlebitis of the Hepatic Veins" and to this series added

FIG. 1. HEPATIC PORTION OF THE INFERIOR VENA CAVA SHOWING THE THROMBI WHICH OBSTRUCT MANY OF THE HEPATIC OSTIA
Note the occlusion of the large right hepatic ostium

another. In his description of the inferior vena cava and the hepatic veins he says "The obliteration was in all cases caused by connective tissue at the ostia, which was continuous with that of the intima of the vena cava. Up to this point the veins were to some extent patent. The obliterating connective tissue was dense, slightly cellular, and in parts contained lacunae filled with blood. Careful search could not reveal any pigment therein, as one would expect to find if the obliterating connective tissue had replaced a primary thrombus. The stenosis which existed in all cases beyond the points of obliteration was due to a proliferation of the intima. Here a thrombus was frequently found

blocking the lumen. The media of the veins was well preserved and ran in an uninterrupted course with that of the vena cava. Nowhere was a break therein to be seen as if trauma had caused a previous rupture of the fibers. The adventitia was also normal. The vena cava often showed a marked depression at the site of some obstructed ostia. Near those sites the connective tissue of its intima was thickened. At one point a partly organized thrombus was attached, but beneath it the connective tissue of the intima continued unbroken."

Thompson and Turnbull (6), in 1912, reported three cases of hepatic obstruction and in this paper introduced the term "Primary Occlusion

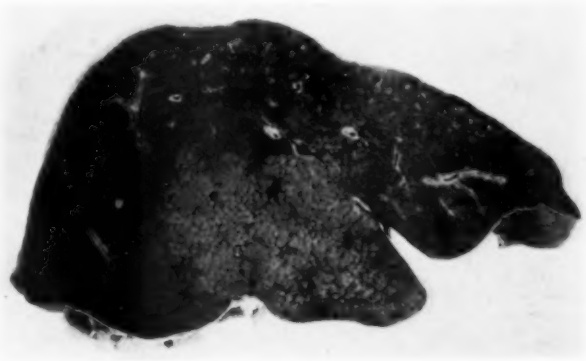

FIG. 2. A CROSS-SECTION OF THE LIVER SHOWING THROMBI IN MANY OF THE EFFERENT VEINS AND THE FIBROSIS WHICH HAS RESULTED FROM THIS OBSTRUCTION

of the Ostia of the Hepatic Veins," stating that "The term 'primary' may be applied to the obstruction at the ostia in this group of cases in order to indicate that the condition is not the result of changes in the surrounding tissues." In two of the three cases of this series, quoting these authors, "The primary pathological condition appeared to be an occlusion of the orifices of the hepatic veins at their entrance into the inferior vena cava and accompanied by partial obstruction of the inferior vena cava immediately below the entrance of the large right and left hepatic veins." The third case was one of septicaemia and showed fresh thrombi in the orifices of the hepatic veins.

The cases cited above showed the obstruction to be almost universally in the hepatic ostia and some pathological changes to be present in the corresponding portion of the inferior vena cava. These observations would suggest that the inflammatory processes were continuous in both vessels. Although Chiari considered his three cases all to be a "Primary Hepatic Phlebitis," there was involvement of the inferior vena cava in two, and in his third case the hepatic obstruction occurred adjacent to the vena cava.

There were many opinions in the literature as to the etiology of this "Endophlebitis Hepatica Obliterans" without definite proof for any.

REPORT OF A CASE

M. A. F., a white female 22 years of age, was seen first at Duke Hospital on January 21, 1932. Her chief complaint was abdominal distention which had been present for one month. At six years of age she had had scarlet fever and at ten years of age she had had influenza. There also had been occasional attacks of severe cramp-like abdominal pain since childhood. In November 1931 there was an attack of abdominal pain which lasted for seventeen days which was relieved when the patient was placed upon a milk diet. There was no history of hemorrhage from any portion of the gastrointestinal tract. The patient was perfectly well except for the above symptoms until April 1928, at which time there were severe generalized headaches which would often persist for a period of one week. Vision became blurred shortly after the onset of headaches and there was noted some diplopia at this time. An ophthalmoscopic examination in May 1929 showed choked discs, and the spinal fluid was under an increased pressure at this time. It was thought advisable to do a subtemporal decompression and at operation the brain was found under tremendous tension. The exact character of the pathological process producing the increase in intracranial pressure was not determined at operation; however, there was a satisfactory relief of symptoms.

The patient's health was good for approximately a year, but at the end of that time there occurred painless abdominal swelling. This abdominal distension increased during the next two or three months and it was necessary to perform repeated paracenteses. In July 1930 a splenectomy was performed. At operation the abdominal cavity was filled with a reddish yellow fluid but, grossly, all the abdominal viscera were normal except the spleen. The spleen weighed 187 grams and in microscopic preparations showed a moderate degree of fibrosis. The histological findings in a biopsy of the liver were those of chronic passive congestion. The sinusoids about the central veins were dilated and filled with red blood cells, although there was no fibrosis in this section of liver. Following the splenectomy there was a normal convalescence except for an accumulation of fluid in the abdominal cavity and edema of both legs.

The patient's health was good during the next 18 months. At this time she had a recurrence of the abdominal swelling associated with severe frontal headaches, the latter being relieved by spinal punctures. There was noted for the first time a numbness along the lateral side of the left arm and in the fourth and fifth fingers of the left hand. This numbness was intermittent in character and was noticed more when the arm had been held for a long time in one position. A sharp pain was occasionally noted in the right hip which usually radiated downward along the lateral surface of the thigh.

The physical examination was essentially negative except for the bone defect at the site of decompression in the right antero-subtemporal region of the skull, and for a positive fluid wave in the abdomen.

The accessory examinations were as follows: White blood count 10,050, with a normal differential; red blood count 4,560,000; hemoglobin 13.5 gm. (94% Sahli); blood pressure 116/96; negative Wassermann on blood and spinal fluid; blood chemistry normal. The spinal fluid was under a pressure of 260 mm. H_2O pressure; the fluid was clear and there were no cells present. The B. M. R. was −22%. The ascitic fluid was cloudy, yellow and had a specific gravity of 1.013. The chemical analysis was as follows: albumin 6 gm. per liter; total protein 1.19 mg.%; cholesterol 65 mg.%. The ascitic fluid was microscopically positive for fats and negative for bile. The Van den Bergh, urobilinogen, and galactose tolerance test were all negative and bromsulphthalein retention was 100% at the end of five minutes and 15% after thirty minutes.

During hospitalization the patient was given a high carbohydrate, low protein, low salt diet with 1.0 cc. salyrgan every two days over a period of five weeks and during this time it was necessary to do four paracenteses with the removal of 16,200 cc. of ascitic fluid.

Nineteen days after discharge from the hospital the patient had a recurrence of her abdominal distention without either edema or jaundice. On readmission 4,000 cc. of turbid yellow ascitic fluid were removed and three days later 3,000 cc. of uniformly reddish fluid were obtained by paracentesis. Examinations of the stools and vomitus were positive for blood which continued to be present until death. 6,000 cc. of turbid yellow ascitic fluid were obtained on the day of death and four hours after this paracentesis there were unmistakable signs of sudden severe intra-abdominal hemorrhage and the patient died twelve hours later.

Report of autopsy

The post-mortem examination was performed three hours after death. In the right temporal region of the skull there was a circumscribed area of softening, which corresponded to the location of the sub-temporal decompression. The brain weighed 1,200 grams and was asymmetrical as the result of the decompression, and in the area of the right cerebral hemisphere were many adhesions. A tumor, approximately 1.5 cm. in diameter, was present on the anterior surface of the pons, loosely adherent to the meninges but not connected with the brain tissue proper; this histologically proved to be a cholesteatoma.

Numerous fibrous adhesions and 2,000 cc. of bloody fluid were present in the abdominal cavity. The posterior surface of the uterus was connected to the rectum by several small bands of fibrous tissue and on the pelvic peritoneum were brownish-yellow areas which suggested blood pigment. A microscopic study revealed a definite pelvic endometriosis with the phagocytic cells containing a non-iron-staining pigment and many crystals which resembled those of bile.

The spleen was absent and many fibrous adhesions were present on the anterior and inferior surfaces of the liver. The latter organ weighed 1,400 grams and was somewhat distorted in shape, this being due either to an accessory lobe, or to an extraordinary mass of newly formed liver tissue on the inferior surface near the mid-line. The greater part of the external surface was irregular, having somewhat the appearance of a "hob-nail" liver. The portal vein showed no evidence of any obstruction.

In an examination of the intra-hepatic portion of the inferior vena cava several thrombi were found firmly attached to the intima, some of which measured 1.5 to 2 cm. in length and extended into the lumen for a distance of 1 cm. Some of the hepatic ostia were obstructed by the thrombi in the inferior vena cava. A probe could be passed for some distance into the left hepatic vein without meeting any obstruction, while the ostium of the right hepatic vein was completely obliterated. Propagated thrombi were present in branches of the hepatic veins which were obstructed by thrombi in the inferior vena cava.

Microscopical sections of the inferior vena cava, removed from near the bifurcation and at the level of the renal veins, were normal, while sections from the hepatic portion showed an inflammatory process characterized by an organized plaque, the outer portion of which was edematous and infiltrated by mononuclear cells, polymorphonuclear leucocytes, red blood cells, and phagocytic cells containing blood pigment. The thrombi were relatively fresh, although some were organized in the orifices of the hepatic veins. No bacteria could be demonstrated in any of the thrombi.

The thrombi in the hepatic veins varied considerably in age, few being completely organized and recanalized. The oldest thrombi were in the portion of the hepatic veins adjacent to the inferior vena cava, and although the thrombi were attached to the vessel walls, there was nothing to suggest an endophlebitis.

The liver showed an increase of fibrous tissue, located most frequently in the central portion of the hepatic lobule, and a considerable regeneration of liver tissue; this combination of lesions resembled a "chronic passive congestion cirrhosis."

There was an apparent increase in the amount of fibrous tissue present in the fat located about the head of the pancreas, and in the microscopic preparations groups of mononuclear wandering cells and organized thrombi were present. Small lobulated areas containing a firm, yellow material, resembling fat necroses were present on the posterior surface of the pancreas, and in the area of the tail of the pancreas the splenic artery and veins were thrombosed.

An ulcer which measured 1 cm. in diameter and 2–3 mm. in depth was present

in the first portion of the duodenum. The base of the ulcer was necrotic and in the adjacent tissues were mononuclear cells and fibroblasts. Gram-positive bacilli and cocci were demonstrated in the bacterial stain of the ulcer.

The contents of the gastro-intestinal tract were brownish black in color, and in the section blood pigment was demonstrated.

DISCUSSION

Weiss (7), in 1929, reported a case of chronic gastric and duodenal ulcers complicated by thrombosis of the inferior vena cava which developed one week after a gastroduodenostomy. The history in our case suggested a peptic ulcer which probably had been present for several years before the onset of ascites and may have served as the focus of infection from which the phlebitis in the inferior vena cava could have arisen. The histological studies showed the inflammatory process to extend from the ulcer into the adjacent fatty tissue about the head of the pancreas. There was no evidence of the infection extending directly by way of any veins to the inferior vena cava, and such a route would not be expected. It has been impossible to estimate the duration of the endophlebitis of the inferior vena cava; however, there were signs of obstruction to the hepatic circulation a few months before the splenectomy in July 1930. The absence of fibrous tissue in the section of liver removed at the time of this operation may be explained on the basis of the short duration of the obstruction. At the same time it must be remembered that the tissue obtained at this biopsy may have been removed from a portion of the liver in which the hepatic vein had been obstructed only a short time.

The recurrence of ascites can easily be explained on the basis of a partial or complete occlusion of the ostia by thrombi of different ages and the thrombophlebitis of the hepatic portion of the inferior vena cava. The edema of the lower extremities and the pathological changes in the liver were due to the venous obstruction in the vena cava and hepatic veins. Although collateral circulation was often conspicuous in cases formerly reported, in our case there was none, the hepatic circulation, while considerably diminished having been adequate to prevent the development of visible accessory channels.

The cholesteatoma was not associated in any way, as far as we could determine, with the endophlebitis. This type of tumor is rarely seen in man, constituting only 0.37 per cent of a large series of brain tumors

reported by Cushing. Bailey (8) is of the opinion that cholesteatoma is not a brain tumor proper but a meningeal growth. It may occur anywhere on the base of the brain, although the favorite location is beneath the pons and mid-brain, whence it extends up into the cerebellopontine angle.

Sampson (9) in this country has contributed most to our knowledge of endometriosis. He is of the opinion that the endometrial implants sometimes have their origin from the endometrium of the uterine cavity, and pass out through the fimbriae of the tube during menstruation to become implanted on the pelvic peritoneum. This endometriosis we regard, of course, as totally unrelated to the vascular disturbance which is the burden of our study.

SUMMARY

1. The literature on "Endophlebitis Hepatica Obliterans" is reviewed to determine whether or not such a lesion ever exists in the absence of a phlebitis of the hepatic portion of the inferior vena cava.

2. A case is reported in which both lesions are associated.

3. The majority of instances in which "Endophlebitis Hepatica Obliterans" occurs as reported in the literature were in association with inflammation of the hepatic portion of the inferior vena cava, and there is little support for the opinion that the two processes are different. Furthermore, there appears to be little, if any, justification for the view that "Endophlebitis Hepatica Obliterans" is a distinct disease entity.

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THE PERSISTENCE OF IMMUNITY AFTER THE ABOLITION OF ALLERGY BY DESENSITIZATION

ARNOLD R. RICH, FREDERICK B. JENNINGS, JR.,[1] AND LILLIAN M. DOWNING

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The tissue hypersensitivity (allergy) which is so commonly acquired during bacterial infections of all sorts has long been widely believed to be a condition essential for the increased resistance to the growth and the invasion of the bacteria (immunity) which the state of infection ordinarily confers upon the previously susceptible body. It has been assumed that it is the accelerated and exaggerated inflammation of allergy which, in the immune body, is primarily responsible both for the prevention of spread of the bacteria and for their more efficient destruction. This belief, although applied indiscriminately to bacterial infections in general, arose largely out of the close association of allergy and immunity in tuberculosis in the guinea-pig—the infection (and the animal) on which most of the work on the relation of allergy to immunity has been carried out. From the study of tuberculosis in the guinea-pig there came the familiar conclusion that allergy and immunity always parallel each other in intensity—the conclusion which has formed the strongest support for the belief that "immunity is achieved through allergy." It should be remembered, however, that there has never been an experiment placed on record in which allergic inflammation has been shown to be necessary for the successful operation of immunity under any condition whatsoever, whether in tuberculosis or in any other infection. On the other hand, it was pointed out several years ago by one of us (1) (2) that, contrary to the prevailing opinion, there were many very good reasons for believing that allergy and immunity in tuberculosis do not always parallel each other, either in the guinea-pig or in the human being; and since it is generally recog-

[1] Died March 29, 1932.

nized that allergic hypersensitivity is all too commonly responsible for damage and death of tissue, it was thought to be a matter of first importance to attempt to determine definitely whether or not acquired immunity to bacterial infection can operate effectively in the absence of the exaggerated tissue damage and inflammation which is attendant upon the allergic state. The familiar untoward local and general effects of hypersensitiveness in bacterial infections, while keenly deplored by all, have nevertheless been regarded as unfortunate but unavoidable evils attendant upon the immunity mechanism. This attitude has undoubtedly discouraged a more intensive search for safe and efficient methods of therapeutic desensitization in the case of bacterial allergy, for according to the belief that allergy is necessary for immunity, to free the body from allergic hypersensitiveness would, *pari passu*, destroy immunity. Further experimental studies from this laboratory, however, have made it perfectly clear that allergic inflammation cannot be regarded as essential for the successful operation of acquired immunity, for in a study of different types of infection it was found that in both active and passive immunity resistance to infection can be cleanly separated from allergic hypersensitivity. On the one hand, it was shown that potent active immunity could be established without the concomitant development of allergy (3), and, on the other hand, that the immunity of allergic, immune animals could be passively transferred to normal animals without the concomitant transference of hypersensitivity (4). These experiments left no doubt that immunity could function efficiently in the face of millions of lethal doses of the bacteria in the complete absence of allergic inflammation; but since it has so often been stated that at least when allergy does exist together with immunity it must then be regarded as an essential part of the immunity of that body, the present experiments, of which an abstract has been published elsewhere (21), were undertaken to determine directly whether or not the hypersensitiveness of the immune, allergic body could be suddenly abolished without entailing a corresponding loss of the body's resistance to infection. It is obvious that such information should form the basis for any studies on the therapeutic effects of desensitization in bacterial infections.

In order to ensure the persistence of the state of desensitization during the entire period of the experiment, we chose infections which run

their course to a fatal termination in non-immune controls within a period of hours. We used the skin as the site of infection so that the development of the lesions could be carefully watched, and in certain experiments the areas of infection were removed at intervals in order to study the lesions and the fate of the bacteria microscopically.

Experiments with Pasteurella aviseptica. In our first experiments we used *Pasteurella aviseptica*, for the reason that this bacterium is extremely virulent for the rabbit, and Jones had shown that immunity can be established by vaccination with killed organisms (5). The vaccine was prepared by washing an 18-hour growth from ascitic agar with physiological salt solution, heating for one hour at 60° in the water-bath, centrifugalizing and resuspending the killed bacteria in salt solution until a turbidity matching an arbitrary standard, which insured a heavy suspension of bacteria, was obtained. The vaccine was prepared fresh each time. One cubic centimeter of this vaccine was injected subcutaneously on two successive days. Five days were allowed to lapse and the two successive injections were repeated. This was continued until a total of ten injections had been given. In some experiments intracutaneous injections of 0.1 cc. of the vaccine were also given with the subcutaneous injections in the attempt to increase hypersensitivity. Both the subcutaneous and intracutaneous injections were made on one side of the body, in order to leave the opposite side for the test infection. Most rabbits immunized in this manner are able to survive the intracutaneous injection of one hundred million lethal doses of the bacillus. We soon found, however, that intracutaneous infection of the immunized animals often produced lesions which differed little in *size* from those in controls receiving the same infecting dose. Now the presence of hypersensitiveness is manifested by a more marked degree of inflammation and tissue damage at the site of infection (as compared with controls) *during a particular length of time*, which is different in different infections. The progressive ulceration of the skin which occurs in a non-immune animal following the intracutaneous injection of tubercle bacilli, for example, may at length surpass in size the allergic ulcer of the Koch phenomenon, but the latter reaches its maximal size much sooner. In the case of infections which run a more rapid course than tuberculosis, and in which the proliferation and disintegration of the infecting bacteria

proceed more rapidly than in the case of the slowly multiplying tubercle bacillus, the allergic response may be correspondingly accelerated. This is clearly evident in pneumococcal infection in the rabbit, as we shall see in a moment. In any event, in order to determine whether or not an allergic reaction occurs on re-infection, it is necessary carefully to observe the lesions in the immunized and control animals from hour to hour. If allergy is present, at some point the local lesions in the allergic animals will be distinctly more inflamed, or larger and more necrotic than those in the controls. Later, the free proliferation of the bacteria in the controls may cause their lesions to become much larger than those in the allergic, immune animals, whereas the lesions in the latter will remain stationary in size and gradually undergo retropression because of the death of the contained bacilli. It is therefore clear that unless the local lesions are watched carefully until one has learned at what period to expect the allergic reaction, the occurrence of the reaction may be entirely overlooked. It is quite a mistake to assume that allergy in all infections resembles the tuberculin reaction in that the lesions need not be observed until twenty-four hours have elapsed. In acute infections the allergic reaction may be at its height within seven to ten hours and at twenty-four hours the lesions in the controls may far surpass it in size. Furthermore, it is evident that a number of factors aside from the degree of allergy may influence the ease with which the presence of allergy can be detected. These factors are those which tend to influence the size and rapidity of development of the lesions in the controls. In the first place, the rapidity with which the bacteria can proliferate in the non-immune body and the degree to which their proliferation is checked in the immune, allergic one will play a decided rôle. If, for example, proliferation is very rapid in the non-immune body and greatly restrained in the immune one, it is obvious that after the lapse of a given length of time following infection the lesion in the non-allergic body may, by reason of the vastly greater numbers of bacteria at the site, be quite as large as the allergic lesion in the immunized body in which far fewer bacteria are present because of the restraining forces of immunity. Again, if the bacteria elaborate toxic products which damage tissue locally, the effect of the toxin in the non-immune body in which the bacteria grow freely may produce a lesion which at any point of time after infection will be as

large as that resulting from allergy in the immune body, in which bacterial growth is restrained and any toxin produced promptly neutralized.

In the case of *Pasteurella aviseptica* infection in the rabbit we found that at least one, and possibly both, of the above mentioned factors which tend to mask the presence of allergy enter prominently into the picture. The rapidity of multiplication of this bacillus in the tissues of the non-immune rabbit is astonishing. Sections of lesions removed several hours after injecting the bacilli show great clouds of innumerable bacilli. In addition, although the existence of an exotoxin associated with this microörganism has not been satisfactorily established, it is perfectly clear from microscopical studies that it gives rise to products which are very potent in producing rapid necrosis and liquefaction of tissue. These two facts, therefore, bring it about that local lesions produced in the non-allergic animal by this bacillus develop rapidly. During the first hours, however, the site of infection, although oedematous, is very pale. In contrast, the lesions in the immunized animals, although often no larger than those in the controls, are usually deep pink in color. From the macroscopic appearance during the development of the lesions in most cases, therefore, while there is little differences in size between those of the immunized animals and those of the controls (some of the lesions in the immunes may actually be smaller due to the fewer bacilli which they contain), generally there is a distinctly earlier appearance of inflammatory hyperaemia in the immunized group. Bacterial stains of lesions removed at frequent intervals show that at each stage there are many more bacilli in the lesions of the controls. Since in the early hours of the infection the lesions in the immunized animals are as large as those in the controls, even though the former contain fewer bacilli, it is clear that the immunized animals must be hypersensitive to the bacteria. Indeed, a few animals in every series developed hypersensitiveness to such a degree that at each stage of the infection the local lesions were several times as large as those in the controls. The presence of hypersensitivity can also be brought out by injecting killed bacteria instead of living ones, thus eliminating the factor of bacterial multiplication. Although even the dead bacilli exert a definitely toxic effect upon the tissues of the normal animal, the lesions produced by a given dose in

the immunized animals show a distinct degree of inflammatory hyperaemia and oedema at a time at which the sites of injection in the controls are still pale. The actual diameter of the lesions, however, although much larger in occasional very hypersensitive immunes, is often even smaller than in the controls, and in such cases the only distinguishing mark of hypersensitiveness is the earlier appearance of inflammatory hyperaemia. The fact that, with a high degree of immunization, the lesions produced by saline suspensions of dead bacilli are often smaller in the immunized than in the normal animals, suggests, at least, a neutralization of a toxic product contained in the bacilli. This requires further study. If such be the case, the lesions in the immune body would represent almost entirely the effect of hypersensitiveness.

From what has been said it is clear that although the immunized animals tend to react, dose for dose, with the accelerated tissue damage and inflammation of allergy, this tendency may be largely masked when comparison is made with non-immune controls for reasons discussed above. However, since hypersensitiveness is evident, we proceeded to attempt to abolish it by desensitization, and to study the effect of such treatment upon immunity to infection. In order to effect desensitization we chose the method of large intravenous injections of killed vaccine. It was to be expected from our previous studies that severe constitutional reactions would be produced in many of the rabbits, leading to the death of some of them. The hypersensitivity of the survivors, however, should be greatly depressed or abolished by the treatment. When a series of animals had been thoroughly immunized by repeated subcutaneous and intracutaneous vaccination with killed cultures, therefore, half of the group were given an intravenous injection of 5 cc. of a freshly prepared concentrated suspension of heat-killed bacilli in saline. Most of the animals became groggy and ill immediately following the injection. A few died within an hour. Others died several hours later. The majority, however, quickly recovered from the effects of the treatment, and on the following day were given a second intravenous injection of 5 cc. of killed vaccine. Severe reactions were less common following this second injection. Several hours later the treated animals, the untreated immunes and normal controls were given intracutaneous injections of a 20-hour culture of virulent bacilli. One-tenth cubic centimeter of a 1–100

dilution was injected at two different sites so that one lesion could be removed for microscopic study when desired, and the other left as a test of immunity. In addition, 0.1 cc. of culture diluted 1–1,000, 1–10,000 or 1–100,000 was often injected at a third site in order to observe the reactions to smaller doses. The sites of infection were carefully watched following the test infection, and blood cultures were made at frequent intervals.

The results of the experiments were very interesting. We shall describe only the reactions at the sites of injection of the 1–100 dilution. The reactions to the smaller doses were correspondingly less prompt and prominent. In the normal controls a pale, slightly oedematous lesion one or two centimeters in diameter was always plainly evident between one and two hours after the injection of the bacteria. The lesions at this time in the immunized, undesensitized animals were the same size or, in some cases, larger and in addition were distinctly hyperaemic and oedematous. In contrast, the desensitized group of immunized animals showed no lesion at all at the site of infection. Several hours later the lesions in the controls had increased in diameter by about a centimeter and had begun to acquire a pale pink color. Those in the undesensitized immune animals were either the same size as before or slightly larger, but the oedema was ordinarily greater and the color often an angry red. At this period the sites of infection in the desensitized group were still free from visible reaction. There was neither oedema nor hyperaemia. At nine hours after infection the lesions in the controls had about the same diameter but hyperaemia was more pronounced. There was at this period little difference between the appearance of the lesions in the controls and in the undesensitized immune animals. In many of the desensitized immune animals still no lesion could be seen, but in a few of this group a minute, slightly elevated lesion, several millimeters in diameter, and pale pink in color was present. At twenty-four hours the controls were either dead or dying. Their average period of survival following infection was twenty hours. Few lived as long as thirty hours. The lesions at the time of death were often haemorrhagic and ulcerated. At this time the lesions in the undesensitized immune animals often had necrotic centers, and ulceration with the discharge of creamy pus was common. All of the desensitized animals showed lesions at this period,

but they were much smaller than those in the undesensitized immune group. From this point the lesions in both the undesensitized and desensitized immune animals gradually regressed to complete healing. All of the controls developed septicaemia; the blood cultures of both the undesensitized and desensitized immunized animals remained consistently sterile, with the exception of an occasional animal in each group which, because of insufficient immunity, succumbed to the infection. Table I summarizes the survivals in the various groups.

Microscopically, it was found that, as has been pointed out by one of us in the case of other bacteria (6), the bacteria always multiply for a while even in the most highly immune body. In both the undesensitized and densensitized immune animals, therefore, multiplication proceeds during a period of several hours following infection, so that in

TABLE I

Infection of rabbits with Pasteurella aviseptica

	NUMBER INFECTED	SURVIVED	DIED WITH SEPTICAEMIA	PER CENT SURVIVED
Desensitized immunes	38	33	5	86.8
Undesensitized immunes	26	21	5	80.7
Non-immune controls	28	0	28	0

sections taken after a lapse of three hours there are many more bacilli in the lesions than were deposited there. Proliferation of the bacilli is much more marked in the lesions of the non-immune control animals, however. In all three groups an inflammatory outpouring of polymorphonuclear leucocytes has begun as early as an hour after infection, and increases steadily during the succeeding twenty-four hours. At nine hours there is little difference between the amount of inflammation in the controls and that in the undesensitized immunes, and thereafter the extent of inflammation in the former surpasses that in the latter because of the prodigious growth of the bacteria in the one and the suppression of their growth in the other. From the beginning, and throughout the course of the infection, however, the amount of inflammation in the desensitized group is *far less* than in either of the other groups. We have said that for a number of hours after infection it is ordinarily impossible to see any appreciable macro-

scopic local reaction whatever in the desensitized group. It is of considerable importance to record, however, that a very definite, though relatively small, amount of inflammatory exudate is present at the site, microscopically, from the beginning. In the undesensitized immunes a large area of oedema with necrosis and liquefaction of tissue is rapidly produced, and this becomes bordered by leucocytes. In the central oedematous, necrotic area are found the multiplying bacteria. In contrast, in the desensitized animals the corium is soon diffusely infiltrated with leucocytes which are everywhere in contact with the bacteria, which they avidly phagocytize, but oedema and necrosis of tissue are very slight in amount. The leucocytes steadily increase in numbers until at length a minute abscess is formed. The degree of destruction of tissue and inflammation at each stage is insignificant as compared with that in the undesensitized group (Figs. 1 through 6); however, the small amount of inflammation which does occur is thoroughly effective in restraining successfully the growth of the bacteria, and in destroying them. It must be remembered that undoubtedly much of the inflammation in the undesensitized group is a response not to the bacteria themselves but to the necrotic tissue, and as such is superfluous from the standpoint of immunity to infection.

In these experiments, then, the desensitized animals maintained their immunity to infection in the complete absence of allergic inflamtion. The inflammation at the site of infection was always *far less* than that in the controls or in the undesensitized immunes, and the destruction of tissue was also insignificant in the desensitized animals as compared with that in the undesensitized ones. Immunity, however, remained intact in spite of the comparatively slight reaction. We wish to reiterate that the bacillus used in these experiments is extremely virulent for the rabbit. When a culture is diluted to the point that plates shown an average growth of only three colonies for each tenth of a cubic centimeter plated, a tenth of a cubic centimeter of that dilution injected intracutaneously always produces a fatal infection. It is therefore highly probable, as has been noted by other investigators, that one single bacillus injected intracutaneously would produce a fatal infection in the non-immune rabbit. In 0.1 cc. of an average twenty-hour culture of this organism there are at least 300,000,000 bacilli. One-tenth cubic centimeter of a 1–100 dilution (the dose used

in the above experiments) represents, therefore, about three million lethal doses. We have carried the test of immunity even further in two series by using 0.1 cc. of undiluted culture as the infecting dose, *i.e.*, one hundred million lethal doses. The desensitized animals remained immune in the complete absence of any allergic reaction. Their lesions, as before, were *far smaller at each stage* than those of either the controls or the undesensitized immunes. From these experiments it is clear that the exaggerated inflammation of allergy is not necessary for the successful operation of immunity in this infection.

Experiments with the pneumococcus. The use of the pneumococcus in experiments of the type just described at once obviates all difficulty in determining the presence of hypersensitiveness such as we were confronted with in the case of *P. aviseptica* infection. Intracutaneous vaccination with killed cultures of pneumococci establishes a very high degree of allergy, which is beautifully brought out by the subsequent intracutaneous injection of either living or dead organisms. Although active strains of the Type I pneumococcus are extremely virulent for the rabbit (dilutions of culture showing only two or three colonies per 0.1 cc. when plated, quite regularly cause fatal infection when this amount is injected intracutaneously) the multiplication of this microörganism in the body is not nearly as rapid as that of *P. aviseptica*. Sections of lesions taken at the same periods following infection with approximately the same number of organisms in each case, show a far greater growth of *P. aviseptica*. Whether this slower growth of the bacteria in the non-immune body is primarily responsible for the more striking contrast between the allergic reactions and the control lesions in the case of pneumococcal infection, on the basis of the principles discussed above, whether the toxic principle elaborated by the pneumococcus (7) is less potent than that associated with *P. aviseptica*, or whether the degree of hypersensitivity to the pneumococcus is simply far greater, it remains true that reinfection of animals immunized intracutaneously with this organism gives rise to the most brilliant and unmistakable allergic reactions. This development of cutaneous hypersensitivity was described by Julianelle and Avery in 1928 (8), and has been studied at length by one of us in other connections (4) (6) (9). Pneumococcal infection, therefore, provides a most excellent opportunity for the study of the relation of hypersensitiveness to immunity.

In these experiments the method of procedure was essentially the same as that outlined above in the experiments on *P. aviseptica* infection. The rabbits were immunized by intracutaneous vaccination with heat-killed Type I pneumococci which were highly virulent for the rabbit. In the preparation of the vaccine the pneumococci were washed from ascitic fluid agar plates with sterile saline until a fairly heavy suspension with a turbidity approximately equal to that of an arbitrary standard was obtained. The saline suspension was heated at 60° for 40 minutes in a water-bath, and was then concentrated ten times by centrifugalization and resuspension in one-tenth the original volume of saline. This final heavy suspension was always tested for sterility by inoculation into ascitic fluid broth or on ascitic fluid agar plates. The vaccine was made fresh before each inoculation. Only one side of each animal was used for vaccination, the other side being saved for the test infection. One-fifth cubic centimeter of the vaccine was injected intracutaneously on two successive days, after which a period of five days was allowed to lapse before the next two injections. This procedure was repeated until a total of ten intracutaneous injections had been given. Hypersensitiveness becomes plainly evident after several injections have been given, and at the end of the treatment the final injections of vaccine provoke very marked allergic lesions. Thus, several hours after the injection of 0.2 cc. of vaccine, normal controls have practically no reaction at the site, while in the vaccinated group there are at this time well developed erythematous, oedematous lesions several centimeters in diameter. Twenty-four hours later the controls have pale slightly elevated lesions about 1.5 cm. in diameter. In contrast the vaccinated animals have oedematous, inflamed lesions as large as 4 cm. in diameter which, in most cases, show a central area of necrosis.

Desensitization was effected by the same method as that in the *Pasteurella aviseptica* experiments. Five cubic centimeters of the unconcentrated suspension of killed organisms were injected intravenously, followed by 5 cc. on the following day. Some of the animals received only one intravenous injection, and that several hours before the test infection. The test dose was 0.1 cc. of a 1–5 dilution of a 15-hour blood broth culture of Type I pneumococcus, of a virulence such that several diplococci would kill a normal control. The test infection,

therefore, was at least ten million lethal doses. This amount of culture was injected in two separate places so that one site could be removed when desired for microscopical study and the other left as a test of immunity.

The effect of the desensitizing injections on the character of the response to infection was most striking. Three hours following infection the undesensitized immunes showed definite allergic lesions which were much larger and more inflamed than those in the controls. At this time no lesion at all could be seen in the desensitized animals. At seven hours most of the desensitized animals still showed no macroscopic lesion, although an occasional one had a slight reaction at this time. In no case, however, were the reactions in any way comparable in severity with those of the undesensitized group, and they were likewise smaller than the lesions in the controls which, at this time, were well established but still less marked than those of the undesensitized group. At 24 hours the diameter of the allergic lesions was, on the whole, somewhat smaller than at seven hours. The oedema and hyperaemia were, however, even more marked (Fig. 8). In contrast, the lesions in the desensitized group were extremely slight. Indeed, in several animals no macroscopic lesion at all could be seen (Fig. 7). Most, however, showed a spot of slight, and often very vague, erythema without oedema, about 2 cm. in diameter. The controls at this time had the usual large purpuric lesions spreading over the entire side, which are characteristic of Type I pneumococcal infection in the rabbit. Blood cultures were at no time positive in either the desensitized or the undesensitized immune animals. The blood cultures of the controls were positive at seven hours and thereafter, and all the animals of this group died before forty-eight hours.

Table II summarizes a typical protocol. Table III shows the total number of animals studied.

There is no need to dwell upon a description of the microscopic appearance of the lesions removed at different periods after infection other than to say that at each period following infection the amount of inflammation in the desensitized group was always *less* than it was in the controls. Obviously, therefore, there occurred neither the accelerated nor the exaggerated inflammation of allergy. The lesions in the undesensitized animals, on the other hand, showed up to seven

TABLE II

Typical protocol of experiment showing character of local lesions in undesensitized immune, desensitized immune and non-immune control rabbits following intracutaneous injection of Type I pneumococcus

TYPE OF RABBIT	3 HOURS	7 HOURS	24 HOURS	OUTCOME
4 Undesensitized immunes	6½ x 2½ cm. Oedema. Erythema*	6 x 3 cm. More oedema and erythema*	4½ x 2½ cm. Marked oedema. Florid*	Regression. Survival
	4½ x 2½ cm. Oedema. Erythema*	5 x 2 cm. More oedema and erythema*	2½ x 2 cm. Marked oedema. Florid*	Regression. Survival
	4½ x 3 cm. Oedema. Erythema*	3½ x 2½ cm. More oedema and erythema*	4 x 3 cm. Marked oedema. Florid*	Regression. Survival
	3½ x 2 cm. Oedema. Florid*	4 x 2 cm. More oedema and erythema*	3½ x 2 cm. Marked oedema. Florid*	Regression. Survival
4 Desensitized immunes	No lesion visible*	No lesion visible*	2 x 2 cm. No oedema. Slight erythema*	Regression. Survival
	No lesion visible*	No lesion visible*	2 x 2 cm. No oedema. Vague erythema*	Regression. Survival
	No lesion visible*	No lesion visible*	No lesion visible*	Regression. Survival
	No lesion visible*	2½ x 1 cm. Slight oedema. Pale*	5 x 1½ cm. No oedema. Slight erythema*	Regression. Survival
3 Non-immune controls	No lesion visible*	6 x 2½ cm. Slight oedema. Pale pink‡	10 x 3 cm. Oedema. Purpuric‡	Died before 48 hrs.
	1 x 1 cm. No oedema. Slight erythema*	3 x 2 cm. Slight oedema. Pale pink‡	10 x 5 cm. Oedema. Purpuric‡	Died before 48 hrs.
	2 x 1 cm. No oedema. Slight erythema*	4 x 2 cm. Slight oedema. Pale pink‡	8 x 3 cm. Oedema. Purpuric‡	Died before 48 hrs.

* Blood culture sterile.

‡ Blood culture positive.

hours a much more intense inflammation and destruction of tissue than those of the controls. The unrestricted proliferation of the bacteria in the controls and the destruction of the bacteria in the undesensitized immunes permitted the lesions in the former to surpass those in the latter after this lapse of time. This was easily seen in bacterial stains of the lesions, for whereas very few pneumococci could be found in the lesions of the desensitized and undesensitized immune animals at seven hours after infection, there were at this time hordes of cocci in the lesions of the non-immune controls. Although, as we have said, the lesions in the desensitized group were macroscopically and microscopically insignificant in comparison with those in the other two groups (Figs. 9, 10, 11), it is important to emphasize the fact that in the desensitized group there always occurred a steady infiltration of leuco-

TABLE III

Infection of rabbits with Type I pneumococcus

	NUMBER INFECTED	SURVIVED	DIED WITH SEPTICAEMIA	PER CENT SURVIVED
Desensitized immunes	14	14	0	100
Undesensitized immunes	14	14	0	100
Non-immune controls	15	0	15	0

cytes into the corium where the bacteria were deposited. It is of great interest that this inflammation, slight as it was, was nevertheless quite sufficient to bring about the effective destruction of the bacteria, the maintenance of a sterile blood stream, and the survival of the animal.

From these experiments it is perfectly clear that, in the complete absence of allergic inflammation, immunity to virulent infection remains intact in the face of several million lethal doses of pneumococci. We have used doses ten times as large in exactly similar experiments with the same result, but we used the 1–5 dilution in most of our experiments because the differences between the allergic lesions and those in the controls are more clearly brought out when the test dose is not so massive that it stirs up the rapid development of a lesion in the controls. We have not carried the test of immunity to more extreme lengths, for it is highly unlikely that anything approaching the number

of bacteria used in these experiments is ever suddenly deposited at one spot in the tissues in natural infection.

DISCUSSION

The experiments on pneumococcal and pasteurella infection reported in this paper demonstrate that the capacity for reacting with the accelerated and exaggerated inflammation of allergy can be abolished by the intravascular injection of killed bacteria, and that in animals so treated immunity to millions of lethal doses of virulent, living bacteria remains intact in the complete absence of allergic inflammation. To what extent it is proper to designate the desensitization effected by the method as specific desensitization cannot be stated with certainty, for a non-specific element is undoubtedly present. This is particularly true in the case of the experiments with *P. aviseptica*, for we have found that the intravenous injection of killed cultures of this organism will prevent completely the occurrence of an allergic inflammation in animals sensitized to the pneumococcus. Rabbits which have been rendered immune and allergic to the Type I pneumococcus are as effectively desensitized by *P. aviseptica* vaccine as by pneumococcal vaccine, and such desensitized animals, when reinfected, retain their immunity in the complete absence of allergic inflammation. Indeed, the amount of inflammation which occurs in normal rabbits at the site of infection with *P. aviseptica* is greatly diminished by an intravenous injection of killed organisms given several hours before the test infection. Such animals, however, die in the same period of time as do untreated animals infected with the same dose. The pneumococcal vaccine given intravenously also has some power in reducing the amount of inflammation at the site of infection in normal animals, but it is not nearly so potent in this direction as is the *P. aviseptica* vaccine. These observations make it clear that there is at least a non-specific element in the action of the vaccines administered intravenously. The precise meaning of "specific desensitization" is, of course, not at all clearly understood. In the case of hypersensitivity to non-bacterial foreign protein it is well known that one can abolish the anaphylactic (musculospasmodic) type of hypersensitivity by an intravenous injection of the specific antigen, and the allergic (necrotizing-inflammatory) type of tissue hypersensitivity to non-bacterial foreign protein (Arthus phenom-

enon) can likewise be abolished by the same method. It was because of this that we chose the intravenous injection of bacteria as the method of abolishing bacterial allergy in the present experiments. However, hypersensitivity to non-bacterial foreign protein can also be depressed or abolished by the intravenous injection of a variety of substances other than the specific antigen, and this we found to be true of bacterial allergy as well. It must be remembered that the mechanism of so-called "specific desensitization" is not at all properly understood, nor do we really know whether it is so very different fundamentally from non-specific desensitization. One can recite very resonable theories relating to the saturation of antibody by antigen in the case of specific desensitization, but actually all that we are able to say with certainty as to the mechanism is that "specific desensitization" is a term applied to the abolition of hypersensitivity by means of the injection of the particular antigen to which the body is sensitized, and that "non-specific desensitization" is a term used to designate the abolition of hypersensitivity by means of the injection of substances other than that particular antigen. However, these are questions which, although extremely important for the problem of the perfection of more satisfactory methods of desensitization for therapeutic use, do not at all effect the particular point with which the present experiments deal —*i.e.*, the demonstration that neither the prevention of spread of bacteria, nor their successful destruction, is dependent upon the occurrence of allergic inflammation at the site of infection.

The very slight amount of inflammation which, in the desensitized immune animals, was able to protect the body against the attack of millions of lethal doses of virulent bacteria was really astonishing. The important fact brought out by the microscopical study of the lesions was that in the presence of the humoral forces inherent in the condition of acquired immunity there is no need for an *exaggerated* inflammatory reaction. The humoral antibody reinforces the protective mechanism of inflammation so powerfully that not only is an increased amount of inflammation such as occurs in an allergic reaction unnecessary, but complete protection is afforded by an amount of inflammation *far less* than that which occurs in the non-immune body. The presence of opsonin enhances tremendously the protective power of the leucocytes in their function of ingesting and destroying the bacteria, so that a few

leucocytes in the immune body are more powerful than thousands in the non-immune one; and as for the prevention of spread of the bacteria in the immune body, which has been assumed to be effected by the exaggerated inflammation of allergy, one of us has recently shown in pneumococcal infection that this is primarily the effect of the immune antibody, and is completely independent of allergic inflammation (6). The present experiments serve to confirm that work, for the spread of the bacteria through the tissues and into the blood stream was prevented just as effectively in the desensitized animals, in which allergic inflammation was completely absent, as it was in the highly allergic group.

Although the amount of inflammation necessary to protect the immune body is astonishingly slight, and distinctly less than that which occurs in the non-immune body, nevertheless we wish to emphasize strongly the absolute necessity of that slight amount for the protection of the body; for Rich and McKee have shown, in pneumococcal infection, that if the leucocytes of an immunized animal are reduced by treatment with benzol to the point that none migrate to the site of infection, the bacteria, although they are held fixed for a long time at the site by the action of the immune antibody, nevertheless continue to multiply progressively, and eventually produce a fatal septicaemia (10). On the other hand, in those experiments, as in the present ones, it was a matter of astonishment how few leucocytes were necessary to effect the destruction of the bacteria, for when only a relatively slight infiltration of leucocytes appeared at the site, the bacteria were promptly engulfed and destroyed.

The present experiments, as well as those mentioned in the introduction to this paper in which immunity was separated from allergy by different methods (3) (4), demonstrate clearly that *the function of the immune state in regard to inflammation is to enhance greatly the protective power of the inflammatory mechanism, with the result that much less, rather than much more, inflammation is required to protect the body from infection.* This, indeed, is an obvious corollary to the results of the many *in vitro* studies on the protective effects of leucocytes and immune serum. Furthermore, in all of these experiments in which allergy was eliminated from the picture, the bacteria were effectively destroyed with a minimum of damage to the tissues of the body. The action of

acquired immunity in the absence of allergy is, therefore, comparable to the action of natural immunity, in which the bacteria are effectively destroyed with only slight inflammation, and with only a negligible damage to the tissues. It must be clearly recognized that a great part of the inflammation which occurs at the site where bacteria lodge in the allergic body is not directed against the invading bacteria, but is purely a response to the damage which the tissues have suffered because of their hypersensitivity. It is the inflammation which occurs at any site at which tissues are damaged and killed by whatever means. Furthermore, the progress of allergic inflammation does not cease with the death of the bacteria. Much of it really only begins when the products of the dead bacteria are liberated, and microscopic studies, therefore, show that the allergic damage and inflammation continue to progress after all stainable bacteria have disappeared from the lesions. A very clear idea of the amount of inflammation which the immune body finds necessary to direct against the bacteria themselves can be obtained by a study of the tissues in these three types of experiment in which the complicating effect of allergic damage to tissue was eliminated; and, as we have said, that amount is remarkably slight. In the light of these facts the destruction and the limitation of spread of the bacteria cannot be regarded as dependent upon allergic inflammation, for the experiments presented here, as well as those of a different type reported elsewhere (3) (4) (6) make it clear that both the destruction and the limitation of spread of the bacteria will be accomplished effectively at the same site, in the same manner and to the same degree, when the allergic part of the reaction is completely abolished.

Several years ago when the first experiments of the series of studies of which the present paper forms a part were published (1), there was a rather general agreement that allergic inflammation is necessary for the prevention of spread of bacteria, and for their successful destruction in the tissue of the immune body; and hypersensitiveness was widely regarded as a proper measure of immunity. Questioning voices had, indeed, been raised from time to time on the basis of various clinical observations which did not fall in line with that view, but no direct evidence one way or the other had been brought forward. Since then, however, in addition to the studies from this laboratory, experimental evidence that immunity is independent of allergy has been brought

forth by other investigators, working with a variety of different infections. Among these may be mentioned the studies of Swift and his coworkers (11) and of Clawson (12) on streptococcal infection, of Julianelle (13) and of Francis and Tillett (14) on pneumococcal infection, and of Branch and Cuff (15) on tuberculous infection. In addition, the results of the present experiments on the separation of immunity from allergy by desensitization have been extended to tuberculous infection by Rothschild, Bernstein and Friedenwald in this laboratory. They have shown clearly that, in the guinea-pig, acquired resistance to virulent tubercle bacilli remains intact in the face of complete desensitization maintained continuously throughout the experiment (16). The very interesting reverse side of the problem has recently been exposed by Seibert (20) of the Henry Phipps Institute for the Study of Tuberculosis, and by Sabin, Smithburn and Geiger (17) of the Rockefeller Institute. These investigators have kindly permitted me to quote from their papers which will appear shortly. Working independently, they established a high degree of tissue allergy to tuberculoprotein by sensitization with the purified protein, which was originally isolated and shown to be the active constituent of tuberculin by Long and Seibert (18) (19). When their allergic animals were tested for immunity by the injection of living bacilli, however, it was found that far from being more resistant to infection, they were actually more susceptible. The duration of life in the allergic animals was shorter and the destruction of tissue greater even than that in normal controls which received the same infecting dose. Indeed, each time that a crucial test has been applied to the question, allergy and immunity have been found to be independent and dissociable phenomena. The results of Sabin and her co-workers and of Seibert are particularly interesting in connection with the cases of tuberculosis in the human being, especially in childhood, in which a high degree of allergy is present in the face of a very low degree of resistance. The negro also provides a striking example of this state, for it is obvious to anyone who has the opportunity to study tuberculosis in this race that, whereas the negro develops a very high degree of hypersensitivity, as a rule he lacks the ability to develop immunity to the same degree as the white, and as an adult city-dweller he cannot maintain satisfactorily the immunity which he does develop. Pinner and Kasper, who have recently re-

studied this matter carefully, state that their results "lead necessarily to the conclusion that infection tends to produce a high state of allergy in the negro, but that he, unlike the white, does not readily acquire a state of increased resistance coincidently" (23); and Cummins has arrived at the same conclusion from his recent studies of tuberculosis in the South African negro, in connection with the extensive investigations of the British Commission (24).

The question of the part played by allergy in bacterial diseases is by no means merely an academic one. In tuberculosis, the injurious effects of allergy have long been obvious to every student of the disease, but they have been regarded as regrettably unavoidable accompaniments of the immune state. In numerous other infections the presence of allergy is well recognized, but its effects have been less thoroughly studied. There is a little doubt, however, that the importance of those effects in the pathogenesis of the many bacterial diseases in which allergy makes its appearance will become more and more apparent as the investigation of the subject progresses. Numerous suggestive facts in this connection come readily to mind. It is interesting, for example, that in syphilis, in spite of the fact that the spirochaetes are disseminated widely through the tissues as early as several days after infection, extensive destruction to tissue does not take place until the later stages of the disease, and it is in the later stages that allergy first makes its appearance. Again, in typhoid fever the bacilli after ingestion enter the blood stream with great rapidity (22), and circulate freely in the blood and are widely disseminated throughout the tissues from the beginning; but ulceration of the intestine, and the profuse and characteristic necroses in the liver, spleen, marrow and lymph nodes occur only later. Does the allergy which is known to develop in typhoid fever during the febrile period play a rôle in this destruction of tissue? It is important to know precisely. But it is also important to obtain a better understanding of the exact mechanism of allergy, in order that safer and more efficient methods of protecting the body by means of desensitization can be perfected for use not only in asthma, hay fever and food allergy, but also in those bacterial diseases in which it is determined that allergy exerts harmful effects. Perhaps in some bacterial infections under some conditions allergy may be necessary for the protection of the body; but that it is necessary has never been

demonstrated in any infection under any condition. Therefore, until its value has been demonstrated, and not merely postulated by attractive reasoning, it would seem wiser to treat it as it plainly manifests itself—*i.e.*, as a condition which increases the susceptibility of the tissues to the damaging effects of the products of bacteria liberated during infection—and this especially in the light of the studies which have made it clear that the presence of hypersensitiveness is not necessary for the operation of immunity

SUMMARY

Experiments were carried out on *P. aviseptica* and pneumococcal infection in order to determine whether immunity would be any the less efficient after the abolition of allergy by desensitization.

When the capacity for reacting with allergic inflammation is completely destroyed by the injection of large doses of killed bacteria into the veins of hypersensitive, immune animals, immunity to intracutaneous infection with millions of lethal doses of living, virulent bacteria remains intact. Inflammation at the site of infection in such animals is far less in amount than in untreated allergic, immune animals—far less, indeed, than in normal controls; but the bacteria are prevented from spreading from the site, and are as effectively destroyed as they are in the allergic, immune body. The immune state acts to enhance so greatly the protective power of the inflammatory mechanism that much less, rather than much more, inflammation is required to protect the body from infection. Damage to tissue at the site of infection is also far less in the desensitized animals than in the allergic ones.

Even in the highly allergic, immune body, therefore, allergic inflammation is not necessary for protection against infection, and in its absence the body is protected with much less damage to tissue than that which occurs in the allergic body.

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EXPLANATION OF ILLUSTRATIONS

(Photographs by Mr. Milton Kougl)

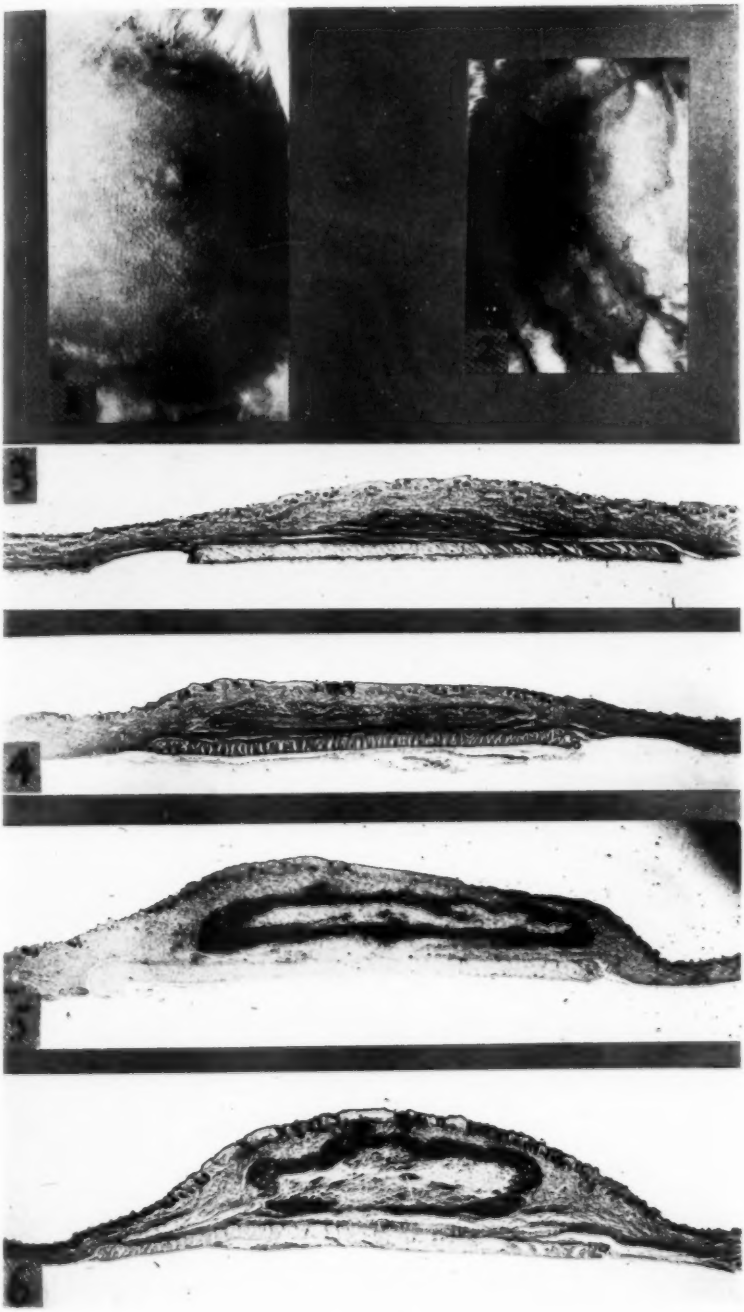
FIGS. 1 AND 2. Twenty-four hours after injection of 0.1 cc. of a suspension of killed *P. aviseptica* into the skin of a desensitized, immune rabbit (Fig. 1) and an allergic, immune rabbit (Fig. 2). The lesion in the allergic animal is much larger, boggy and red, in contrast to the small, paler nodule in the desensitized one. The latter, when tested previous to desensitization, had reacted to the same degree as the animal of Figure 2. Both of these animals belonged to the exceptionally hypersensitive group mentioned in the text.

FIGS. 3, 4, 5 AND 6. Low power microphotographs (all are of same magnification) of lesions produced by living *P. aviseptica*, showing the small amount of inflammation and necrosis in desensitized immunes as compared with that in undesensitized immunes. All four animals were immunized at the same time in the same manner, as described in the text. All lesions were removed 20 hours after infection, at which time the normal controls receiving the same dose were dead. Figure 3 is a desensitized immune rabbit infected with 0.1 cc. of a 1–100,000 dilution of living culture. Figure 5 is an undesensitized immune which received the same dose. Figure 4 is a desensitized immune infected with 0.1 cc. of a 1–100 dilution, and Figure 6 an undesensitized immune which received the same dose. The large area of necrosis and liquefaction of tissue in the undesensitized immunes (Figs. 5

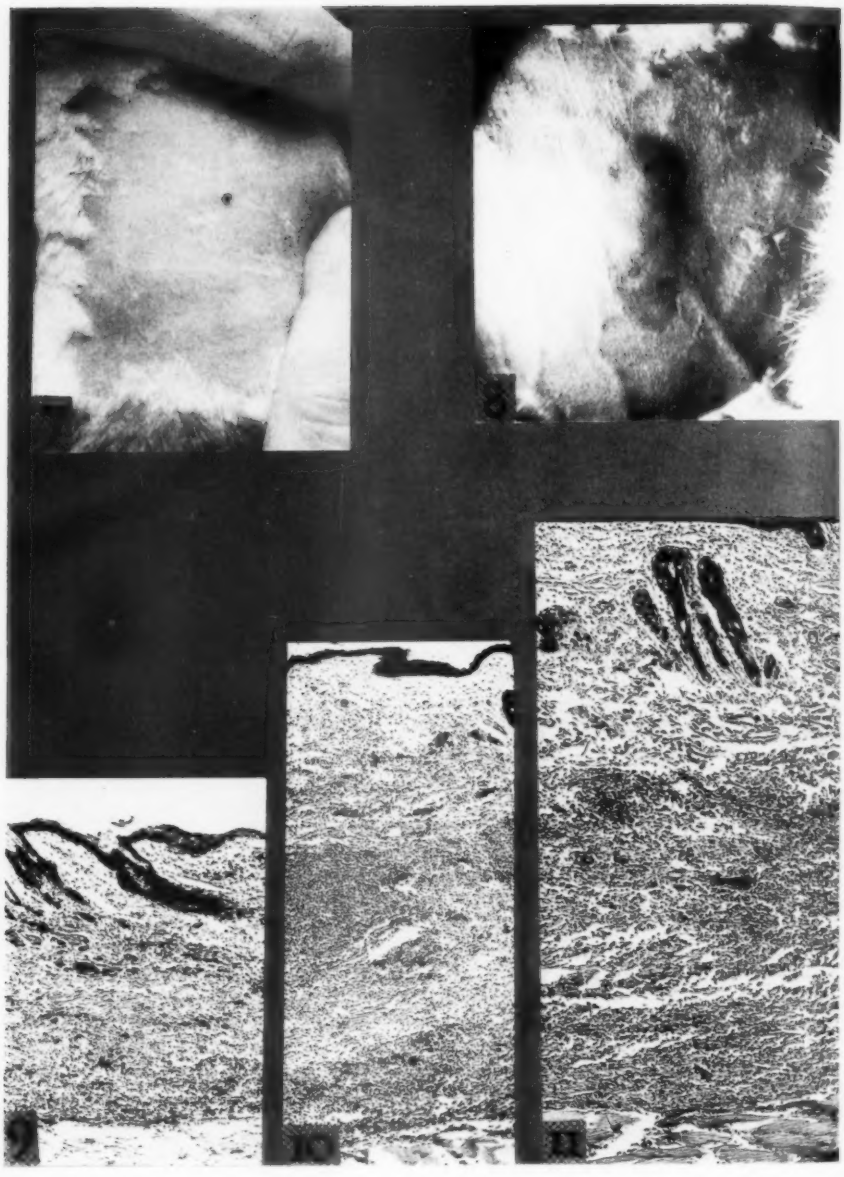
and 6) is plainly visible. In sharp contrast, inflammation and necrosis in the desensitized immunes (Figs. 3 and 4) are relatively slight, and yet entirely sufficient for complete protection, as shown by the fact that the animals survived the same dose of bacteria injected simultaneously at a different site and left as a test of immunity.

FIGS. 7 AND 8. Twenty-four hours after the injection of 0.1 cc. of a 1–5 dilution of living culture of Type I pneumococcus into the skin of a desensitized immune (Fig. 7) and an allergic immune rabbit (Fig. 8). There is practically no lesion visible at the site (marked by an ink spot) in the desensitized animal which, previous to desensitization, had been tested and had reacted with a marked degree of allergy. In contrast, a large, oedematous, red lesion is present in the undesensitized animal.

FIGS. 9, 10 AND 11. Microphotographs (all are of same magnification) of the local lesions in a desensitized immune (Fig. 9), a control (Fig. 10) and an allergic immune rabbit (Fig. 11) seven hours after the intracutaneous injection of 0.1 cc. of a 1–5 dilution of living culture of Type I pneumococcus. The lesion in the allergic animals shows necrosis and liquefaction of the entire corium, with intense inflammation. The lesion in the control at this time shows well developed inflammation, but less necrosis and less inflammation than in the allergic one. The lesion in the desensitized immune animal shows a diffuse infiltration of the corium with inflammatory exudate, but there is far less inflammation than in either of the other two, and necrosis is minimal in amount. The relative degree of distension of the tissues with inflammatory exudate can be appreciated by comparing the distances between the muscle beneath the corium and the surface epithelium. There are swarms of pneumococci in the lesion of the control, but they can be found only with careful search in the lesions of the allergic and the desensitized animals. The relatively slight amount of inflammation in the desensitized animal was entirely sufficient for complete protection, as determined by absence of bacteraemia and by survival (the same dose of pneumococci was in each case injected at a different site and left as a test of immunity). The blood culture of the control was positive at the time the lesion (Fig. 10) was removed, and the animal died within 36 hours.



Figs. 1–6



FIGS. 7–11

FOCAL CELL REACTIONS IN TUBERCULOSIS AND ALLIED DISEASES

Being the William Sidney Thayer and Susan Read Thayer Lectures for 1933

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PART I. THE EPITHELIOID CELL REACTION

In a problem as complicated as the relation between two living organisms intimately associated as host and parasite—a problem repeated with variations in every infectious disease—the mode of approach determines more or less the information obtained, and with many factors remaining unknown the results of inquiry may differ radically. The experimental method of analysis conveniently pursued in modern laboratories has dominated the field of operations. The final goal, however, is an understanding of the manifestations of the disease as a whole, that is, as it occurs spontaneously. To bridge the gap, the experiment must approximate the natural disease ever more closely, but the experiment itself becomes thereby more complicated as the model approaches the natural condition to be imitated.

Tuberculosis has been exploited chiefly by the use of cultures and culture products of the tubercle bacillus on animals, more particularly by observing the results of inoculations and injections upon normal and partly immunized animals. Latterly, it has been aided directly and indirectly by tissue cultures. Thus far the comparative method has not had its proper share in the analytic problem. The bovine disease has been all but neglected. The spontaneous disease in monkeys has not received the attention it deserves. In the animal forms of this disease, all stages are accessible to study. Though the comparative study of spontaneous tuberculosis has its weak points and defects, the experimental study is not free from them. It suffers from several difficulties which become conspicuous when we endeavor to transfer results to the spontaneous disease. In all cases alien hosts

are used, the bacilli are more or less saprophytized, the dose administered is enormous compared with the single bacillus starting the natural focus. The natural channels are circumvented by direct inoculation and the general manifestations of a diseased state are highly exaggerated and distorted. The habit of accelerated multiplication of the saprophytized or culture bacilli acquired on artificial media is carried over into the inoculated animal. Both in this regard and with reference to the metabolites and the somatic substances, the experimental disease is influenced by a fairly extensive shift of these substances as compared with the spontaneous disease, and this changed concentration cannot but have a distinct influence on the type of cells stimulated and the course of the local reaction. The speeding culture bacillus becomes more vulnerable with increasing growth acceleration. The quantity and quality of the tissue reaction change. Phagocytosis becomes modified in extent or in the character of the participating cell groups.

The most outstanding work illustrating the effects of the different constituents of the tubercle bacillus as isolated and determined by Anderson has been recently published by Sabin and her associates (1). Briefly stated, "the lipoid portion of the organisms, notably a phosphatide constituent, possesses the capacity of producing tubercular tissue, *i.e.*, epithelioid cells and giant cells. The so-called waxes cause a proliferation of fibroblasts. The acetone soluble fat induces proliferation of all connective-tissue cells and of blood vessels, and causes hemorrhage. The polysaccharide is chemotactic for and toxic to leucocytes. The protein is responsible for fever and in addition causes a proliferation of plasma cells." The task of correlating the relative part played by these building stones of tubercle bacilli in the spontaneous disease starting with a single, living bacillus still remains to be done. In what follows I have adhered as far as possible to the spontaneous diseases and to a considerable degree inferences drawn from the material accessible differ from those on record. The literature of tuberculosis is enormous and it is quite possible, and indeed assumed, that concepts and ideas to be presented have been repeatedly published by others.

The dominant activity of infectious agents in the acute diseases is first local and is followed by invasion of the blood and secondary focal

lesions, if the host survives. The local activity rises with the chronicity of the disease and the focal lesion becomes the important center of activity for both host and parasite. The invasion of the blood is in abeyance until the host begins to fail. With the development of the primary focal lesion two factors appear; first, the active participation of the local tissue cells and some general influence emanating from the primary focus which modifies certain cell groups in the entire system and produces both an increased resistance of these cell groups to subsequent invasion as well as a heightened sensitiveness designated as allergy. This general systemic influence gives rise to cell disturbances often of diagnostic value in the living animal. In clinical medicine the rise and decline of mobile cell groups in the circulating blood has been focused upon because it is the readily accessible part. It represents a disturbance to be explained by some focal process, usually a concentration of parasites or bacteria and certain host cells. What goes on in these concentration camps is not the whole story of the host-parasite conflict, but it represents the major share of that conflict. The leucocytic formula of the blood is a mere index of it.

In animal diseases the focal gatherings of such cells are more easily approached, because animals may be killed at any stage. The focal gathering of polymorphs leading to abscess formation is the most frequently observed occurrence. The remarkable chemotactic affinity of eosinophile cells for animal parasites is always a striking phenomenon. Myriads of these cells, often migrating *en masse* through intact epithelial layers, gather in the presence or in the wake of some living parasite and form veritable eosinophile pus. They do not appear to undergo the disintegrative changes observed in the focal aggregations of the neutrophile cells. The regular appearance of lymphocyte gatherings in certain pathological and post-pathological states is also a familiar occurrence. It is pertinent to inquire whether the chemotactic response of these cells is due to more than one substance, or whether there is some one common ingredient or component in the various stimulating agents that governs the gathering of these three cell groups and accounts for their special movements.

In the endeavor to formulate in a general way the cell movements in the presence of infectious and parasitic agents, I have conceived the activities of both host and parasite as offensive or aggressive and

defensive or protective, without assuming any purposeful behavior on the part of either. These two groups of activities, developed through trial and error methods of nature, range themselves under humoral and under immediate cellular activities on the part of the host, and under metabolic, diffusible, and under cell-bound or somatic substances on the part of the parasite. Those substances of the parasite secreted and discharged during life and finding their way throughout the host organism must be met by humoral substances, either naturally on hand or produced under stress by cell groups as are antitoxins. Those bound to the parasite would be met by contact with or ingestion by host cells. This grouping or classification of reciprocal, interacting forces agrees well with the antiblastic theory first presented by Ascoli (2) and developed experimentally by Dochez and Avery (3). The humoral factors inhibit certain vital functions of the parasite or neutralize their injurious action, and certain host cells then ingest and intern the parasite, either gradually disintegrating it or allowing it to die of inanition.

Aschoff (4), in a discussion of inflammation, distinguishes between a general and a local defensive reaction. The general reaction includes fever, leucocytosis, and antibody production; the local reactive processes involve parenchyma, vascular system, and supporting tissue framework. Applying this theory to the foci of cell reactions as developed in certain diseases, we may further postulate that cell aggregations forming abscesses are in a sense equivalent to phagocytosis by single cells. In the abscess it is the interaction of large numbers of one or several types of cells with or without phagocytosis which not only protects the rest of the host system from invasion, but which also protects, in a sense, the parasite, for here the bacteria may be found in large, often immense numbers, whereas the rest of the system is sterile. Any breaking away of the abscess contents internally would continue the disease. The abscess either discharges its contents outwards, or the contained bacteria gradually decline in numbers and eventually die out.

All studies of focal cell reactions have revolved around tuberculosis, that classical example of a focalized disease. Yet the immense amount of patient research centering in the tubercle has not brought unanimity in the interpretation of its various phases. The variables

involved presenting a different aspect with every approach lead to diverse views. If we study experimental tuberculosis in guinea-pigs, our views will differ from those of others who study it in rabbits. Human tuberculosis differs slightly from bovine, and both distinctly from avian tuberculosis. We arrive at varying results according to the cultures we use, the age of the strains, the period allowed for the span of the experimental disease. Finally, experimental tuberculosis is definitely governed by the number of bacilli introduced.

It has been my good fortune to have had under observation for a number of years two infectious bovine diseases which have many characters in common and many divergent. Bovine tuberculosis and paratuberculosis are sufficiently alike to have induced the first students of paratuberculosis to describe it as tuberculosis. Only when the bacillus could not be cultured on media on which bovine tubercle bacilli will multiply, and when laboratory animals failed to respond to inoculation, was the non-identity recognized. A comparative study of the lesions of the two bovine diseases, supplemented by the isolation and culture of the two types of acid-fast bacilli, brought to the surface a few suggestive facts which I am using as a basis for certain inferences. Several other diseases have been drawn into the comparative study, and the result is a kind of rounding up of miscellaneous observations extending over years.

Although bovine tuberculosis has played such a conspicuous rôle in the operations of public health agencies as well as in the economics of agriculture, and the bovine bacillus such a prominent part in experimental studies designed to throw more light on the human disease, comparatively little has been written on the main, obtruding characters of the spontaneous disease. The relatively short life of cattle eliminates to a large degree long-standing superinfected or reinfected types. A number of years ago (5) I pointed out that if all individuals of a herd of cattle infected with tuberculosis are killed at any one time, a large number—in some herds towards 90 per cent—is in the early lymph-node stage. The respiratory form predominates over the intestinal form, although pastured animals may have tuberculosis of the retropharyngeal and mesenteric lymph nodes which suggests alimentary infection. In the respiratory form the dorsal, mediastinal and bronchial nodes are involved. The lungs themselves

are in many cases entirely free. When foci occur, they are not limited to the apical lobes but may be found in any lobe, chiefly, however, in the most expansive diaphragmatic or lower lobes, clearly indicating direct aerial infection. Foci in different stages and therefore evidence of infection at different times are absent. Rarely, caseous pneumonia follows the aspiration of discharging primary foci into other regions of the lungs. In the dorsal mediastinal nodes, the primary infection is frequently manifest in small tubercles, 1 to 2 mm. in diameter, situated in the zone in which carbon and dust particles are deposited. These I assume are due to a single bacillus or a compact mass of a few bacilli carried thither from an alveolus by way of the lymphatics. Unfortunately, the earliest pre-necrotic stage I have not seen. To the naked eye the small tubercles in this stage simulate the normal tissue closely and are overlooked. This primary tubercle, when first detected, consists of the irregularly jagged necrotic center, an enveloping zone of epithelioid cells, gradually giving way to fibroblasts, and an outer distinct capsule of these cells. Giant cells are usually absent from the primary tubercle. Similarly, tubercle bacilli are scarce and frequently searched for in vain.

Many researches have been focused on this primary seat of tubercle bacilli, but since it comprises the life of two quite different organisms, the host cell and the tubercle bacillus in intimate contact, two quite different types of cell metabolism and the eventual, rapid or slow destruction of both cell and bacilli, the final interpretation of the building up and the involution of the tubercle must await much more penetrating cell studies than are available at present. All we can do is to encircle the problem a little more closely and propose suggestions which may or may not point in the effective direction.

Leaving for the moment this disease and turning to the second bovine disease due to acid-fast bacilli indistinguishable morphologically from tubercle bacilli, we are confronted with certain suggestive likenesses and differences (6). The activities of the paratubercle bacillus are limited to the mucous membrane of the intestines, extending in some animals to the submucosa and always to the mesenteric lymph nodes. The disease starts in the lower ileum and spreads in both directions, reaching both the duodenum and the rectum in certain active types of the disease. The degree of infiltration and swelling of the mucosa

depends on factors of resistance and virulence. Disease may be slight and not recognizable with the naked eye, or the swelling may be extreme. The mucosa is then thrown into large thick longitudinal and transverse folds. There is no evidence of loss of epithelium or ulceration. Clinically, the disease manifests itself in the form of intermittent or persistent watery discharges and progressive emaciation. There is no definite thermal elevation. Among the regularly appearing reactions found at autopsy is an extensive phagocytosis of red cells in the spleen and gradual conversion of the inclusions into pigment. Evidently the red cells are damaged while circulating in the capillaries of the intestinal villi. More rarely, extensive necrosis of the fat deposits in the abdomen is seen and this is probably due to the infiltration of the mucosa around the papilla of the pancreatic duct, resulting in partial obstruction of the latter.

The histological picture is fundamentally the same in all cases examined but it varies in degree and intensity. In the rapidly advancing type of disease, the entire intertubular tissue of the mucosa consists of cells of epithelioid type. A zone of similar cells, broad or narrow, may be found in the submucosa. In the stationary, resisting type a small focus of epithelioid and giant cells occupies the distal or free portion of all or of only a certain percentage of the villi. When extending to the large intestine the process involves the same tissues. The intestinal tubules, with exceptions to be given, are intact. The mass of epithelioid cells has crowded out all lymphocytes and eosinophile cells normal to this tissue. Applying the carbolfuchsin stain and decolorizing with acids, or acids and alcohol, we find that every cell having epithelioid characters contains acid-fast rods of quite uniform size and slightly shorter than tubercle bacilli. This difference in size largely vanishes in cultures, however. The number of bacilli within cells may be so great that the cell itself appears as a dense red mass. Since this occurs in animals killed and promptly autopsied, it is not the result of post-mortem multiplication. In the restricted disease with small foci in the villi, bacilli are always present in the cells but are few in number. Although the epithelioid cells may be loaded with bacilli, they appear normal when stains, such as hematoxylin, are used which do not bring out the contained obscuring bacilli. In eosin-methylene blue sections the bacilli may be detected as ex-

cessively minute bluish points in the cytoplasm. As stated above, the mesenteric nodes are always invaded. Epithelioid cells filled with bacilli occupy the follicles and cords and tend to obliterate the peripheral lymph channels through expansion and pressure. The size of the nodes is not, however, appreciably increased.

Among the differences noted in the cell reactions manifested in the presence of tubercle and paratubercle bacilli, the irregular, indefinite extension of the epithelioid tissue in paratuberculosis, as contrasted with the focal, definitely limited spherical structure of the tubercle, is noteworthy. A second differential character is the total absence of necrosis or caseation even in the most extensive infiltration of paratuberculosis. Associated with these characters is the absence of any tendency to fibrosis or to bounding or limiting the epithelioid areas by capsule formation. The respective seats of the local disease in the two diseases differ strikingly. The failure of the paratubercle bacilli to multiply beyond the mesenteric lymph nodes is not explainable at present. The favorable nidus in these nodes should be present in lymph nodes elsewhere, unless some special product of digestion is needed which might not be available beyond the mesenteric nodes themselves.

The differences in these two diseases cannot at present be correlated with what is known of the bacilli. The paratubercle bacilli do not produce a progressive disease in laboratory animals which are susceptible to the tubercle bacillus. Slight local lesions may be produced and some of the injected bacilli recovered in cultures months later. The culture of the paratubercle bacilli failed on media which favored multiplication of the tubercle bacillus until Twort and Ingram (7) pointed out that the addition of dead tubercle bacilli, or extracts, made multiplication possible on egg media and on glycerine agar. Following Twort's procedure and using a suspension of tubercle bacilli boiled in 50 per cent glycerine as an addition to egg media, I have experienced no difficulty in obtaining pure cultures from every animal autopsied.

Naturally, the problem of the origin, source, and nature of the epithelioid cells which form the matrix in which both types of bacilli are found could not be thrust aside, for it has agitated the minds of pathologists since Virchow's day. Baumgarten (8), Orth, Ziegler,

Thoma, and other pathologists regarded the epithelioid cells as derived from the fixed cells of the connective tissue. Metschnikoff regarded the tubercle as a mass of immigrated macrophages. Since the formulation by Aschoff of the reticulo-endothelial system as a collective concept of variously functioning cells of the lymphatic and connective tissue structures, the source of epithelioid cells has been conveniently referred to it. Some writers have been more definite in regarding vascular and lymph epithelium as precursors.

The variations in the cellular reactions of the mucosa from animal to animal affected with paratuberculosis gave rise to certain suggestions as to the development of the epithelioid cell which favored the views of the older pathologists that it arises from cells *in situ*. Most sections present the picture of large areas of epithelioid cells, stuffed with bacilli. The cells may be still with a single nucleus, or they may have two or even more. In certain cases the adenoid reticulum consisting of still fusiform elements also contains bacilli, either incorporated with or attached to the cytoplasm. Similarly, when the still normal membrane near the muscularis mucosæ or the submucosa itself is scrutinized, minute clumps of bacilli may be detected attached to still fusiform elements. These latter may be either alone or already associated with epithelioid-like, bacilli-containing cells. Without drawings it is difficult to convey the appearances. Photographs do not present the details clearly. On the basis of these observations, the theory has gradually taken shape that the epithelioid and its derivative, the giant cell, are produced by contact with the bacilli which stimulate in some way the growth of the cell cytoplasm and eventually become enveloped by it. The epithelioid cell is conceived as a hypertrophic pathological product of a normal cell. It may be rapidly destroyed as in tuberculosis. It may be stimulated in various degrees by the parasitic inclusions or contacts. It is a sick cell with heightened capacity to digest the contents, or soon overcome by the toxic character of the inclusion. The host-parasite cell is thus an unstable product with many degrees of susceptibility and resistance from early necrosis to complete resistance and final indifference to the presence of the bacilli. Each host-parasite combination defines the character of the resulting lesion, its morphology and growth limitations.

If we contrast the cell behavior in tuberculosis and paratuberculo-

sis, certain interpretations appear justified. The spherical, limited structure of the tuberculous lesion indicates some central radiating activity missing in the paratubercle bacilli. The prompt central necrosis may be due either to a high initial fragility of the normal tissue cells in the presence of a toxin, or to a rapid swelling or hypertrophy of the cell cytoplasm checking normal nutrition, or both factors may be at work. The declining concentration of the toxin outward leads to the epithelioid cell mantle and lastly to the fibrous capsule. A high virulence favoring rapid multiplication would lead to dissemination of the tubercle bacilli, before a shutting in of the primary focus, through the system. This occurs in experiments with small animals. The inference is warranted that there is a certain definite relation between the tubercle bacilli and the natural host similar to that of other host-parasite combinations. This relationship manifests itself in the localization and multiplication of the bacilli in certain tissues, as well as in the modification of the tissue cells themselves in the presence of tubercle bacilli. Degrees of immunity and susceptibility disturb this relationship towards greater multiplication of the bacilli or their suppression and towards a changing behavior of the tissue cells. The relation resembles the adjustment of a chemical reaction to a certain equilibrium shifted one way or the other by changes in the concentration of the constituent substances.

In paratuberculosis the evidence points to the absence of any diffusible toxins. The disease progresses by contact of bacilli, which have escaped from infected cells, with fresh tissue cells. In tuberculosis the bacilli appear to influence cells through metabolic products. Epithelioid cells are probably developed without direct contact with bacilli. The general scarcity of bacilli and their absence from most epithelioid cells, unless current staining methods are at fault, warrant this inference. Necrosis or caseation may be the direct result of toxins. When the tubercle bacillus is of a lower order of virulence but of greater persistence, necrosis may be due to the gradual expansion of the epithelioid syncytium which enters a slow nutritional death through gradual blocking of the vascular supply.

It is highly probable that the epithelioid cell has been traced to too narrow an ancestry and that different views among pathologists may in part be ascribed to this conception. It is conceivable that, besides

physiological differences among bacteria, special types of virulence among the same bacteria may bring different cell types into the epithelioid class. A swelling of the cytoplasm and an enlargement or edema of the nucleus with changed condition of the chromatin may approximate different cells to a superficially identical type. In rabbits the pulmonary lesions following injection of bovine tubercle bacilli have in some foci presented to the writer the appearance of alveolar cells becoming epithelioid by an increase or hypertrophy of the cytoplasm.

The course of the two bovine diseases differs, in that paratuberculosis appears to be continuous in its progress, while tuberculosis is saltatory. The tubercle develops and becomes encapsulated, and unless bacilli escape from this primary focus the disease quiets down. When escape does occur, there is a sudden revival of the symptoms with the appearance of a second crop of tubercles. Occasionally, the shock of this secondary attack kills experimental animals, such as rabbits and guinea-pigs, over night. There are however differences between the first and the second stage. The secondary tubercles remain small. Necrosis is less extensive or entirely absent. Giant cells are regularly present. This change in reaction is associated with a changed attitude of the tissues associated with allergy. The well-known tuberculin reaction is a product of this changed state. It is obvious, in view of the appearance of allergy, that besides the local initiating tuberculous process there is a humoral factor issuing from this local focus which influences the entire system and leads to a different behavior of the reticulo-endothelial system and the escaped bacilli towards one another. This partial immunity tends to be ignored because it is partial. Upon it depends any assistance that may be expected from any form of vaccination or serum therapy. Allergy could not develop without the wide diffusion of some diffusible antigenic product of the tubercle bacillus. The more highly parasitic or specialized paratubercle bacillus does not stimulate any allergic condition, and the process does not tend to become self-limited unless genetically predetermined. There is no paratuberculin reaction of sufficient significance to be of any value in diagnosis. The metabolism of the bacillus is of a character which is spent in contact with and within the epithelioid cell, and systemic effects are negligible. Even with extensive disease the temperature is about normal.

The changed tissue reaction associated with and following the primary focus in tuberculosis involves a partial immunity of the entire reticulo-endothelial system. Certain diffusible substances set free from the primary focus evidently affect certain tissue cells every where to become more resistant to certain products of the tubercle bacillus. The necrosis is restricted or prevented. The bacilli from a primary focus, now controlled by certain antibodies, are limited in their activity to the formation of giant cells in which they are lodged like neutral foreign bodies. With the partial or complete neutralization of its offensive or aggressive activities the tubercle bacillus may still have defensive or protective activities within the epithelioid cells which keep it alive for variable periods of time.

In looking about for pathological tissue activities to test the conception of the epithelioid cell as presented, certain cell activities in the bovine intestinal tract aroused my attention. In inflammations of the small intestine the swelling of the distal portions of the villi as a result of lymphocyte infiltration tends to compress the mouths of the tubules. The lumina expand and may become filled with mucus. This peculiar lesion was first observed in the study of scours or early diarrhea in calves. Although not entirely absent in very young animals, the distended tubules were seen in largest numbers in calves from one to two months old and in intestines not macroscopically abnormal. It was at first thought that the distended tubules were open, but serial sections did not confirm this assumption. A certain number of calves go through an early period of intestinal disturbance, due chiefly to multiplication of *B. coli* in the lower small intestine, which may account for the interstitial infiltration observed. The occluded tubules vary more or less in shape, condition of lining epithelium, and contents. The varying size of the lumen is probably due to the quantity of mucus secreted into the tubule, for a few tubules contain only mucus. All the rest are partly or wholly filled with cells which have migrated into them. It is probable that the mucus forms a kind of supporting medium for the invading cells. Most frequently the invading cells are of uniform type, with only a few of other types present. The commonest cell form present is the eosinophile leucocyte which is abundant in the interstitial tissue of the normal bovine intestine. These cells form dense molds filling the lumen, and are in

various stages of disintegration. The second type of cell, often mixed with eosinophiles and in some instances the major type with but few other cells present, is the cell known as macrophage or clasmatocyte. In their expanded state in the empty tubule these cells are nearly circular in optical section and measure about 25 microns in diameter. In sections of fixed tissue the cytoplasm is uniformly bubbly and appears as a meshwork with occasional inclusions of masses of chromatin, probably from ingested leucocytes. It is bounded by a narrow, slightly denser outer zone (ectoplasm). The nucleus is oval with chromatin distributed in small masses on the inner surface of the delicate nuclear membrane. Rare mitoses indicate division after entering the tubule.

The epithelium of the clogged tubules is rarely intact. Most frequently it is flattened and thinned out by compression, particularly in the part nearest the intestinal lumen. It would require much more abundant material with detailed history from birth, as well as certain prenatal data, to formulate an explanation of the preponderance of one or the other migratory cell type in the occluded tubules. Possibly some form of microbic life may have been imprisoned in the tubule to account for the cell type present. In one group of calves the cells maintained the more or less discrete form of the mobile clasmatocyte, but in another they tended towards the epithelioid cell type and giant cell formation. They formed irregular syncytia in which cell outlines were no longer distinct.

Among the changes in the mucosa in paratuberculosis a similar occlusion of tubules presents certain interesting problems. The swelling of the distal portions of the villi where the epithelioid cells first appear naturally tends to compress the mouths of the tubules, some of which become greatly distended. In those cases which are characterized by an active proliferation of epithelioid cells in the intertubular tissue, and in which the distended tubules are embedded within the epithelioid areas, the tubules are the scene of an ingrowth of epithelioid cells. The ingrowth is attached to the basement membrane where the epithelium has disappeared. The ingrowing cells form a coherent mass with an occasional mitotic figure in it. It is not clear whether this mass grows by cell division at the root of the mass and is pushed inward or within the mass and on its periph-

ery. Mitotic figures have been found near the free tip of the mass. That the proliferation proceeds from fixed cells in the subepithelial zone seems well established by the fact that all ingrowths are attached by a pedicle to the subepithelial tissue bared of its covering of epithelial cells and that in some instances there is a cell ingrowth from the greater part of the circumference of the tubule. In paratuberculosis all the ingrowing cells contain bacilli, either few or many, and it is probable that the bacilli are passed on in the division of the cytoplasm to the daughter cells. The entire ingrowth or plug is thus made up of epithelioid cells containing bacilli. There is some evidence that the epithelioid-cell mass erodes the epithelial layer and then pushes its way into the lumen. On the other hand, the free cell, or clasmatocyte, has not been found in relation to any break in the epithelial lining and its mode of entry into the lumen is not known. It was present only in tubules still embedded in normal intertubular tissue. The passage of polynuclear, amphophile and eosinophile cells and of lymphocytes, into the lumen of passages lined with epithelium is effected by a kind of digestive process. The epithelium becomes filled with vacuoles containing these migrating cells. The method used by the larger clasmatocytes has not been seen.

The plugged and expanded tubule presents a kind of tissue culture *in vivo*. There is little doubt that the large cells appearing in the lumen in a relatively normal submucosa, or in a relatively normal environment in a diseased mucous membrane, are clasmatocytes and different from the ingrowing cell mass in a paratuberculous environment. It is difficult to avoid the inference that the paratubercle bacilli are the immediate stimuli to the cell ingrowth. Each cell contains them. It is also difficult not to consider them as derivatives of fixed cells modified by the bacilli within them. A third inference seems warranted, that they are capable of corroding and destroying the superposed epithelial cells. That this corrosion is not going on in many other areas may be due to the fact that the epithelial cells of the plugged tubules are no longer normal.

The total absence of mitotic figures in the main seat of the disease between the tubules and their occasional presence in the ingrowth tempt one to conclude that multiplication is inhibited in the adenoid

tissue by surrounding pressure and that all epithelioid cells there are derivatives of existing reticulo-endothelial cells.[1]

The giant cell as an integral part of the tubercle has held the attention of pathologists, even before the discovery of the tubercle bacillus, when it served as an important diagnostic character. Koch referred to it repeatedly in his monograph. He found it regularly present in the center of the tubercle. Bacilli were always present, even up to fifty or more in some cells. He observed the destruction of giant cells by multiplying bacilli. Today the derivation of giant cells from epithelioid cells or their progenitors is generally accepted. Their presence, however, is not a regular occurrence in tuberculous lesions. In fact, a study of this disease, either spontaneous or induced in different animal species, clearly points to this cell as an indication of natural or acquired resistance, since it is rare or absent in most experimental animals and in the primary bovine foci. In bovine tissues it is regularly present in secondary lesions in the neighborhood of primary foci. The lesion associated with the giant cell is small, occasionally limited to this cell and a mantle of lymphocytes. Necrosis is slight or absent. The cell may be regarded as the result of reduced stimulation by the infectious agent. We have seen that in both tuberculosis and paratuberculosis the epithelioid cell tends to grow into empty spaces by mitotic multiplication. This tendency reduced in intensity would lead to multiplication of nuclei only and a giant cell as the ultimate result. In our examination of tissues the giant cell has contained but few paratubercle bacilli and rarely any in tuberculosis. It is probable that Koch's material was not from an average case of the bovine disease. The giant cell resulting from reduced host-parasite activities may be conceived as the product of a changed disposition of the reticulo-endothelial cell complex. This latter state may be the result of natural resistance or acquired through the dissemination of products from the primary lesion. Stimulation

[1] The tendency to ingrowths in bovine tissues under pathological influence is seen under various conditions. In tuberculosis, ingrowths into the pleural cavity may form very large pendulous masses. Ingrowths from tuberculous peribronchial foci into the bronchi are present in pulmonary tuberculosis. Ingrowths following pneumonia were recently described by the writer (24).

to multiplication of nuclei may occur even in epithelial cells. The writer (9) described intestinal epithelium undergoing multiple nuclear division in the presence of coccidia in the cytoplasm.

The changed reaction of the host tissues to a secondary crop of tubercle bacilli discharged from a primary focus is intimately associated with tuberculin sensitiveness. It is well known that Koch in his early experiments called attention to this changed reaction in the local lesion produced by a second injection of tubercle bacilli. The reaction points to a fixation of the injected bacilli locally, due to an acceleration of the tissue response as compared with the primary reaction. The question whether this allergic condition spreads out beyond the specific infectious agent is of more than ordinary significance. P. A. Lewis and Dorothy Loomis (10) observed that tuberculous guinea-pigs develop much more anti-sheep amboceptor than do controls when given like amounts of sheep red blood corpuscles. Certain heterologous reactions have been observed by the writer in bovine tuberculosis. The carbon pigment coming from the lungs and deposited in the mediastinal and bronchial lymph nodes does not give rise to any unusual cell reaction ordinarily, but in certain nodes having small foci of tuberculosis most of the cells containing the pigment become giant cells. In 1910, the writer (11) published two observations which may be interpreted as a more general allergic condition towards alien material. In a cow inoculated into the thorax with a human type of tubercle bacilli, there was found at autopsy, two months later, on the omentum a flattish, convex, sessile mass of tissue with a circular base about 2 cm. in diameter. The tumor-like mass was pinkish gray. When sections were prepared of the fixed and hardened mass at right angles to the base, it was shown divided into contiguous circular areas, about 3 mm. in diameter, by fibrous tissue. There were about twelve such areas forming the median section. In the center of each was a foreign body readily identified as a nematode in cross-section. Immediately around the body-wall of every cross-section of the worm was a narrow necrotic zone, together with an occasional foreign-body giant cell and some fragments of the worm. The rest of the enveloping zone was made up of lymphocytes. The worm was identified as the common filaria of cattle, normally coiled up in the omentum at a certain stage. The oviducts and uteri

were filled with ova and embryos. In one lung of this animal another roundworm, not identified, had become imprisoned in a mantle of lymphocytes. In another animal which had received several intravenous injections of tubercle bacilli, a similar, smaller worm-tumor was found on the omentum with a filaria buried in it. It might be argued that tubercle bacilli had become lodged near the worm and had given rise to the lymphocyte focus. But, in the first cow, the injection had been made into the pleural cavity where no lesions developed and the characteristic arrangement of cells around every coil of the filaria could hardly be expected if tubercle bacilli had formed the immediate stimuli. The cell mantle was in fact oriented around the body of the worm. This aggressive attitude towards carbon pigment, on the one hand, and animal parasites, on the other, not manifesting itself in normal animals, is indicative of some modified generalized activity on the part of the mobilizable cell groups. This activity may also be accentuated by an especial individual allergic sensitiveness peculiar to certain individuals.

PART II. THE SUCCESSION OF CELL REACTIONS

The variously complex or multiple antigenic structure of parasites necessarily involves cell reactions of different types following one another in the course of any reactive or hostile host-parasite association. Hence we should expect tissue changes in the development and decline of such an association to follow certain definite courses, complicated however by variations in both qualitative and quantitative directions which might obscure the fundamental reactions. In bovine as in human tuberculosis, the tubercle is frequently associated with lymphocytes forming mantles around stationary or subsiding activities of the tubercle bacilli. In paratuberculosis the mucosa is infiltrated with lymphocytes when the primary epithelioid proliferation is slight. In neither bovine disease have polynuclear cell invasions been seen in any stage. The relation of this cell to tubercle formation has been the theme of many students of the tissue reaction in tuberculosis and has recently been discussed by Opie (12). Polymorphs have been associated with the earliest stages of the experimental disease by many observers. Recently Vorwald (13) has emphasized this position following certain experiments. In the

experimental tuberculosis of guinea-pigs following the injection of tissue products containing bovine bacilli or of cultures of freshly isolated bovine strains, the central invasion of tuberculous foci by polymorphs, forming an abscess, was not infrequently noted in animals tending towards an increase in weight. It was thought at first that this late process was associated with definite bovine strains, but this assumption could not be substantiated, since the infiltration could not be reproduced regularly. The late invasion of a tubercle by polymorphs suggests either beginning gradual necrosis of tissue or death of contained bacilli giving rise to special chemotactic substances. The relation of polymorphs to the beginnings of tubercle formation is another question. It is doubtful if it ever occurs in the spontaneous disease. The injection of highly saprophytized bacilli in large numbers into the circulation is a very different procedure from the deposit of a single bacillus by way of the lymphatics into a lymph node.[2]

As a contribution to the general theme, avian tuberculosis was drawn into the field of work. In the spontaneous disease tubercle bacilli are usually very numerous in the central necrotic masses of the focal lesions and in the enveloping secondary tubercles. The necrotic mass becomes a foreign body in the sense that a circle of epithelioid and giant cells encloses it. To modify the natural process, freshly isolated bovine bacilli were injected into a wing vein so as to cause a general distribution of the bacilli. Though the bovine type makes no headway in poultry and the injected animals remain well, certain cell activities in liver, spleen and lungs, indicate the close relationship of the races of bovine and avian types. Minute collections of cells appear in the organs mentioned. They may be entirely lymphoid, or entirely epithelioid, or a mixture of the two cell forms. When the lymphocyte foci appeared first and if the bacilli possessed more than

[2] The writer would make a distinction between tuberculous foci developing in tissues shut out from contact with the exterior, such as lymph nodes, and those developing secondarily in the respiratory, renal, digestive, and genital tracts. In the disease of guinea-pigs due to inoculation with the bovine abortus bacillus, lesions in the epididymis were always associated with suppurative processes, whereas this did not occur in spleen and lymph nodes. Possibly some local filtrable virus may inhabit these exposed tracts and associate itself with the bacteria.

the usual resistance and began to multiply temporarily, epithelioid cells containing bacilli appeared in the center of the small lymphocyte group. If the bacilli did not multiply, no further change took place. Later on, the epithelioid foci appearing with or without preceding lymphocyte gathering were again invaded by lymphocytes as an indication that the active process was over. The appearance of epithelioid centers in the lymphocyte foci is attributed to the swelling or hypertrophy of the cytoplasm of the reticulo-endothelial elements in the focus under the influence of an antigen of the bovine bacilli multiplying abortively and different from that causing the primary lymphocyte gathering.[3]

Some time ago it was pointed out by the writer (14) that whereas the epithelioid foci following injection of the bovine race of *Brucella* into guinea-pigs were not invaded by polynuclear leucocytes, this was quite regularly seen in epithelioid foci due to the porcine race. Such foci might become large abscesses. Here the assigned reasons for the difference were either a rapid proliferation of epithelioids into large foci and hence of less robust character which became necrotic centrally, or the destruction of the enclosed bacilli which gave rise to chemotactic substances. These illustrations bring out the primary phase as that of epithelioid cell proliferation, upon which is grafted the subsequent polymorph invasion. Inasmuch as polymorphs appear sooner or later in most tissue injuries and respond to a variety of chemotactic stimuli, their behavior does not define the condition which preceded their immigration. All that can be postulated is the dual process: first, epithelioid cell production, and second, polymorph invasion—under certain conditions determined either by degrees of local tissue resistance or by bacterial lysis.

A gap would be left in the present discussion if macrophages or clasmatocytes were not included. Their rôle in certain acute infectious diseases has been especially emphasized by Gay (15) and associates in recent years. The invasion of macrophages into closed distended intestinal tubules under conditions departing little from the normal has been mentioned above. Their association with suppura-

[3] In a case of spontaneous tuberculosis in a monkey there was little or no necrosis of the epithelioid center and extensive secondary immigration of polynuclear leucocytes.

tive processes has been widely recognized. When a non-fatal dose of *B. coli* is injected into the peritoneal cavity of guinea-pigs the immigration of polymorphs is followed after a few days by macrophages which ingest the former. In several guinea-pigs the exudation had become a pure culture of macrophages. In experiments designed to trace the source of agglutinins in the cow's udder, living *abortus* bacilli were injected into the udder ducts. Within 24 hours a copious immigration of polynuclear cells into the secreted milk took place. As this subsided, macrophages began to appear in the milk. Any association of macrophages with the local formation or disintegration of tubercles or in the expanding proliferation of epithelioid cells in paratuberculosis was not observed at any time. The macrophage is either tardily stimulated by the agency that promptly calls out polymorphs or is influenced by another substance. It may be stimulated by the degeneration of polymorphs themselves. The late appearance may also be due to the sessile character and the apparently limited and localized supply of these cells. In the illustrations given, the macrophage appears to perform the task of cleaning up or scavengering after the battle has subsided in favor of the host. Views on the sources of the mobile and sessile protective cells of the mammalian host may be expected to differ among cytologists owing to the complexity of the subject and the difficulties surrounding interpretations. Sabin, Doan, and Cunningham (16) regard clasmatocytes as derived from spleen endothelium, while M. R. Lewis and W. H. Lewis (17) consider mononuclears, macrophages, and epithelioid cells as merely different phases (functional variations) of the same cell type.

To trace events in the tuberculous lesion from start to encapsulation presupposes an adequate conception of the fate of the tubercle bacillus in it. As yet it is impossible to give a convincing account of what happens to it. In paratuberculosis it is probable that the numerous bacilli survive in the cells and are eventually cast off. In bovine tuberculosis bacilli are always scarce and frequently not found, although inoculations with tuberculous products are regularly followed by disease in guinea-pigs. Three possibilities present themselves. (a) Multiplication and destruction go on simultaneously while certain bacilli are acquiring a resistant envelope and are finally protected in the necrotic tissue. (b) There is at first rapid multiplication

checked later by immune reactions. (c) Multiplication is restricted from the start and all progeny is preserved for discharge into another host. The last requirement corresponds to a well established parasitism. The abundance of the progeny is adjusted to the losses inevitable in reaching another host. Bacterial diseases, however, are not well established host-parasite associations. The disease itself is an index of the want of balance. Only when evolutionary processes have largely eliminated disease by a proper host-parasite equilibrium can we regard the third condition as prevailing. This condition appears to be more or less attained in the bovine disease, for secondary, generalized infection is rare, and animals can carry a large amount of necrosed tissue with few outward signs of physiological disturbance. The disease is purely local in many animals and evidence of unbalance is due more or less to a highly unnatural environment.

In the experimental disease in guinea-pigs we face an unbalance, leading to prompt or very gradually approaching death, and the bacilli are more in evidence. When guinea-pigs receive a fairly large dose of recently isolated bovine bacilli (0.1 mgm.) into the peritoneal cavity they die within three or four weeks, usually quite suddenly and with thorax filled with a serous fluid. The lesions are represented by groups of epithelioid cells undergoing necrosis and contain many tubercle bacilli. If the dose is smaller and the animal survives this critical period, bacilli are very scarce in the lesions. Under these conditions, especially in the acute type, peculiar forms of bacilli are frequently found. One is the drumstick form, in which one end is swollen into coccoid shape. Bacilli may also appear as two coccoid bodies connected by a feebly outlined rod form, or as acid-fast granules or short segments in line. It is tempting to consider these degenerated forms, although proof is wanting. Recently Gróh (18) has described these granules as the progenitors of new bacilli. The destruction of tubercle bacilli introduced experimentally into rabbits has been thoroughly studied by Lurie (19). Taking available facts as a basis we may infer that tubercle bacilli are actually disintegrated in the surviving epithelioid cells. Secondary, metastatic deposits of bacilli are probably confronted by the reticulo-endothelial tissue made more resistant by antigens discharged from primary foci. Humoral

antibodies may also be given off in the original foci and act directly on the bacilli, for wherever the tubercle bacillus lodges secondarily, the lesions resemble one another and the bacilli are either seen in a certain abundance or not at all. This secondary uniformity of behavior of tissue and bacilli can scarcely be due to anything else than humoral activities starting from the primary focus.

In addition to tuberculosis, paratuberculosis, and infectious abortion in guinea-pigs, epithelioid cell proliferation or stimulation may be present, as a precursor to the polymorph invasion, in what are regarded as acute suppurative processes. The disease in which this form of focal cell reaction was observed is the well-known spontaneous streptococcus disease of guinea-pigs which is readily maintained by contacts. This disease appears in the form of abscesses of lymph nodes which may assume egg size before they rupture. Oral infection induces suppuration of the submental and cervical nodes; infection of the limbs, axillary or inguinal buboes. Suppuration of secondary nodes, such as the bronchial and pelvic nodes, when it occurs, inevitably leads to death. The subcutaneous nodes eventually break and the abscesses disappear, often to be followed by others. The streptococcus appears in chains and is hemolytic in type. For comparative studies a more highly virulent race was at hand which developed under the following circumstances. A group of some twenty guinea-pigs from the same population affected with buboes was brought together in 1917 and kept interbreeding in a small enclosure until 1926. The excess of young was removed from time to time. In the latter year the disease appeared to be lagging in so far as fresh infections were rare. It was feared that the infectious agent might be lost and inoculation was resorted to, with the result that all inoculated animals died within a week. Even placing pus or cultures on a shaven area was fatal. The organisms appeared in the form of clumps, no longer in chains, although cultures from this colony made years before grew in chains. The clumping was ascribed to additional capsule formation. It was also thought that another agent had supplanted the original streptococcus in this limited population, but this view could not be substantiated. Recently the unmodified, non-fatal type was discovered in a foreign population of guinea-pigs, and with this and the highly virulent strain aided by partial immunization, the facts to be described were determined.

In the original description of this disease by Boxmeyer (20) reference is made to monocytes in the lymph nodes. In my own examinations of lymph nodes of guinea-pigs in contact with this disease I frequently encountered areas of cells not to be distinguished from epithelioid cells and so closely resembling those of the *abortus* disease in guinea-pigs that for some time I suspected that the lesions were due to *B. abortus* accidentally introduced. The peculiar condition was finally cleared up when the lymph-node abscesses of the spontaneous disease and those of partially immunized guinea-pigs inoculated with the highly virulent strain were examined. The process in brief may be interpreted as follows. The highly virulent type introduced through abrasions produces foci in which the normal tissue becomes promptly necrotic and an immigration of polymorphs takes place without any phagocytosis. Fresh metastatic foci develop and death comes in four to seven days. In guinea-pigs subject to the endemic type or adequately protected through vaccination towards the highly virulent type, the local process may take a different course. There appear at first groups or foci of cells epithelioid in form, even giant cells. These foci become subject to two subsequent processes, either an immigration and infiltration of polymorph cells, or a necrosis followed by immigration to the periphery of such necrotic foci. It is possible to observe in sections of such foci a groundwork of the epithelioid type of cells infiltrated with polymorphs. The current interpretation would be that we are dealing with a nest of macrophages or clasmatocytes which have taken in the polymorph cells. I was under the spell of this interpretation for some time, but I now regard the polymorphs as having invaded the degenerating epithelioid cells. We have then a process much like that in the *B. abortus* disease of guinea-pigs.

This combination of a central nucleus of polymorphs or pus surrounded by a broad zone of epithelioid cells in which scattering giant cells are present has probably been interpreted by pathologists as primary suppuration followed by the formation of an enveloping zone of cells akin to modified fibroblasts. It will be noted that the interpretation advanced is the reverse. It postulates a groundwork of stimulated epithelioid-like cells invaded later by polymorphs. In a search for an explanation of this dual process we may grant that the super-virulence of one strain of streptococci is due either to a maxi-

mum production of capsular substance or to the production of a second, protective substance also capsular but not identical with the first. The normal guinea-pig is unable to cope with this modified coccus, but by immunization, or when this second hypothetical substance is not produced or the original capsular substance appears in smaller quantity, primary necrosis of tissue is replaced by hypertrophy of the reticulo-endothelial groups of cells and the formation of epithelioid, and more rarely, of giant cells, followed finally by immigration of polynuclear cells and softening of the focus. Placing side by side certain selected microscopic foci, about one half the diameter of a 16 mm. field, from the lymph nodes of guinea-pigs inoculated, respectively, with bovine tuberculosis, *Brucella abortus*, and the streptococcus, we should find difficulty in allocating each one to the proper source of infection. Each one represents a background of epithelioid tissue centrally invaded by polymorphs and the whole surrounded by more or less connective tissue in the form of a capsule. Though the morphological basis of the local reaction is alike in the three diseases, there is no reciprocal immunization. The mechanism is the same but the underlying physiological processes are specifically different.

The modification of the cellular types of reaction in accordance with certain differences in the host-parasite relation, such as a difference in the virulence or antigenic concentrations of the infectious agent, may suffice to account for certain earlier controversies in which both parties were in part right. The kind of lesion produced by the bacillus of glanders was the subject of considerable interest as well as controversy some forty years ago. Baumgarten regarded the glanders nodule as intermediate between a tubercle and an abscess. According to him, the nodule is formed by epithelioid cells derived from fixed cells of connective tissue, vessels, or parenchyma. There follow infiltration from the periphery with leucocytes and the resulting softening and disintegration of the tubercle. From the pus obtained from a fatal case of glanders, J. H. Wright (21) produced the experimental disease in guinea-pigs, and basing himself on an examination of the tissues of these animals, he states that the primary effect of *B. mallei* is not a collection of epithelioid cells but necrosis of the tissues followed by invasion of leucocytes. Later Duval and White

(22) came to a different conclusion. They used a strain which had been attenuated by culture and also raised in virulence by a series of passages through guinea-pigs. A study of the lesions in guinea-pigs developed the fact that the virulent passage culture produces exudative changes, whereas the attenuated form is associated with a tubercle-like structure consisting of epithelioid and giant cells. Certain nodules in the lungs of horses were the subject of controversy, Nocard regarding them as due to glanders, while Schütz (23) looked upon them as parasitic in origin. From our standpoint we should regard both as conditionally right. The horse's lung may contain either or both types of infection in which the histological cellular reactions simulate each other.

The difficulties surrounding a clear conception of the genesis, cell content, and etiology of focal lesions is illustrated in the formidable literature which has grown around researches into the various phases of the liver nodules in typhoid fever. Similar nodules occur in the paratyphoid infections of animals and it is probable that the same stimuli are operative in both typhoid and paratyphoid organisms. My limited histological contacts with the paratyphoid foci lead me to assume that the cells for which this group of bacteria are chemotactic are quite different from those dominating tuberculosis. They suggest endothelial cells overproduced, thrown off, and migrating to form nodules where bacilli have lodged and formed clumps so characteristic of typhoid and paratyphoid bacilli. This interpretation coincides with Mallory's early position. The final solution of this problem can be accelerated by a thorough study of the experimental and spontaneous paratyphoid lesions of animals, since in the human material many unknown and uncontrolled factors exist.[4]

SUMMARY

In the past half century pathologists have been inclined to refer all local cell gatherings to an active resistance on the part of the host. The concept of phagocytosis as a one-sided affair has dominated interpretations. All that we can postulate, however, is that certain bacteria and cell types have an affinity for each other. The outcome

[4] For a full discussion of this cell type see F. R. Sabin and C. A. Doan, *J. Exp. Med.*, 1926, **43**, p. 823.

of such affinity may be death of the host or suppression of the parasite, with various intermediate stages. Certain bacteria, as pointed out, associate themselves with cells of the connective and adenoid tissue which assume epithelioid type. Others like mouse septicemia and the Rickettsia have an affinity for vascular endothelium. The typhoid-paratyphoid groups manifest a chemotactic affinity for endothelial leucocytes. The epithelioid type of cell reaction appears in tuberculosis and bovine paratuberculosis, in glanders, leprosy, and the induced *Brucella* and streptococcus disease of guinea-pigs. It is assumed that the reticulo-endothelial system is the source of these cells. Each group is the product of the specific action of the corresponding infectious agent and the expanding cytoplasm modified specifically, since there is no cross immunization among these diseases. They are the result either of direct contact of the bacteria with the progenitor cell or of diffusible metabolic products, or of products resulting from disintegration or dismantling of the bacteria. The behavior of the epithelioid cell depends upon genetic and acquired host factors, as well as upon virulence of the associated bacteria.

In spontaneous bovine tuberculosis the prompt central necrosis of the tubercle conceals the earliest phases. They are assumed to consist in the multiplication of the deposited bacilli followed by a prompt swelling of the cytoplasm of the local cells and subsequent necrosis. The outward spread and diminishing activity of the metabolic products of the tubercle bacilli lead to the epithelioid-cell mantle and finally the connective-tissue capsule. Multiplication of the cells in the tissues becoming epithelioid is limited or doubtful. Mitoses are not seen. In paratuberculosis the association of bacilli with the normal reticulo-endothelial system is observable and the presence of variously swollen cells ranging from fusiform to typical epithelioid cells can be seen in the progressive disease.

The specifically increasing resistance of the tissues as well as allergy is due to the discharge of diffusible products of the living bacilli and the continuous impact of these substances in minute doses upon the forerunners of the epithelioid cells throughout the system. When bacilli escape from a primary focus, the secondary foci are built under the influence of this increased resistance. They are smaller, with less

tendency to necrosis. Giant cells tend to appear in the secondary manifestations. They are indices of increased resistance in both tuberculosis and paratuberculosis.

From the evolutionary standpoint the gradual loss of diffusible, aggressive metabolic products by the invading parasite reduces the systemic effect and tends to localize and make chronic the disease process, provided the parasite at the same time gains in protective capacity. Host specialization rises and the host-parasite conflict becomes a purely cellular one. Paratuberculosis in cattle and leprosy in man are illustrations of these facts. The one is a progressive, fatal disease, the other one of extreme chronicity. In paratuberculosis the epithelioid cell dominates the field. There is neither necrosis nor fibrosis manifest.

The invasion of the primary epithelioid cell focus by polynuclear leucocytes does not occur in bovine tuberculosis or paratuberculosis. It does appear under conditions not understood in the induced bovine tuberculosis and *Brucella* disease in guinea-pigs and in glanders. There is no evidence that polynuclear leucocytes are involved in the initial stages of spontaneous tuberculosis.

In general the focal lesions in any infectious disease represent the conditions under which the bacterium can multiply and survive and eventually leave the host. Paradoxical as it may appear, these foci, owing to active cell immigrations and proliferations, have been considered the sites where the organisms are suppressed. It is, however, a fact that the same organisms are unable to survive elsewhere in the host, should they break away from the primary focus, unless similar foci are established. This dual nature of the focus as a place where the parasite multiplies and where at the same time it is being opposed by the host must be kept in mind in the interpretation of what can be seen by histological methods. The focus favors both host and parasite and stands for the compromise following interacting attempts at multiplication, on the one hand, and digestion on the other.

All bacteria must first exert some deleterious or stimulating effect on the tissues before a host reaction is set in motion. In the acute infectious disease the reaction promptly follows the immediate action or else the host succumbs. In the chronic affection both stages are drawn out, the action after a time merging into the reaction. The

obtruding action of the tubercle bacillus is necrosis, rapid, gradual, or merging into what appears like stimulation when virulence is low, or genetic resistance when it is high. By low virulence is meant that developed under host-parasite influence and not under artificial culture which is a different process not occurring under natural conditions. Necrosis may thus imply a direct toxic action of tubercle bacilli or a secondary effect following a too highly stimulated syncytium of epithelioid cells interfering with nutrition. In its mildest manifestations the factor underlying necrosis may induce a real stimulation of host-cell growth. All the factors entering into the inner workings of the tuberculous focus are in a state of flux or change, which it is at present impossible to visualize as a whole and which has led to such diverse views, each one exposing some fraction of the actual phenomenon. By defining the conditions, the scope, and the limitations of the problems in hand, all researches will eventually contribute to the final synthetic interpretation of the natural or spontaneous disease.

The idea presented in the foregoing pages is the stimulating activities of the tubercle bacillus. This may manifest itself in many grades of intensity, leading to the development of epithelioid cells, giant cells, the stimulation of fibroblasts, and possibly the direct production of necrosis in high concentration. The epithelioid cell is not related to the macrophage either as to origin or function. It is formed locally through contact of its progenitors with parasites or their products. It differs in these respects from polymorphs which are frankly phagocytic. Their activity amounts to a protection of the host generally, whereas the progenitors of the epithelioid and foreign body giant cells tend to perform this function locally. This idea is in contrast with the concept of phagocytosis which postulates prompt specific aggressiveness on the part of tissue cells. The idea implies, moreover, that immunity tends towards lesser and lesser susceptibility on the part of the cells instead of greater activity, and ending finally in the feeblest reaction the foreign body giant cell. The change following primary infection as manifested in secondary foci is assumed to be associated with antigenic and antibody products discharged from the primary foci which act upon the bacilli in transit and prepare the reticulo-endothelial cells for the secondary encounter. Finally, it

should be emphasized that differences in the histological structure of tuberculous lesions appearing more or less regularly may imply different races of bacilli as well as genetic or acquired differences in the resistance of individuals of the host species. A study of such variations among tubercle bacilli is still in its beginnings.

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BOOK REVIEWS

The Rheumatic Infection in Childhood. By LEONARD FINDLAY. 1932. 187 pp. (*Wm. Wood & Co., New York.*)

Dr. Findlay's book reviews the various manifestations of rheumatic fever and their relative frequency as seen at the Royal Hospital for Sick Children in Glasgow. He does not believe that rheumatic fever is of a streptococcal origin, nor does he believe that upper respiratory infection plays a very important rôle. He suggests the possibility of two strains of the rheumatic virus—one associated with aortic disease and pericarditis; the other with chorea and mitral stenosis; but gives no experimental evidence to support this opinion. By combining the statistics of his hospital with those of a general hospital, Western Infirmary, Glasgow, he gives a composite curve of the mortality rate in rheumatic fever in children and adults, showing two peaks, one in childhood between 10 and 15 years of age and the other between 35 and 45 years. The first peak represents the direct ravages of the disease; the second coincides with the onset of degenerative changes. But this is an expression of opinion.

Dr. Findlay is a strong advocate of bed rest for all early rheumatic infections. His ideal is a minimum of three months in a hospital and a year at a convalescent home for all such cases.

In brief, the book discusses the incidence of various rheumatic manifestations, but adds no new contribution to the subject.

H. T.

The Duodenum—Its Structure and Function, Its Diseases and Their Medical and Surgical Treatment. By EDWARD L. KELLOGG, M.D., F.A.C.S. (*Paul B. Hoeber, Inc., New York, 1933.*)

The author has collected under one cover an enormous amount of data most of which is well selected and correctly interpreted. Naturally in a work of this size there are bound to be subjects on which points of view will differ markedly. The plan of the work may be roughly divided into four sections: (1) anatomy and physiology; (2) diagnostic technic; (3) a description of the various disorders found in the organ and the indications for their medical and surgical treatment; and (4) a long chapter on surgical procedures.

It is in the third section that the major claim of the book's value is found. Herein are tabulated in meticulous detail the age, incidence, x-ray findings, congenital variations, case histories, etc., of such subjects as duodenitis, abnormalities of shape and position, diverticulosis of the duodenum, internal and external fistulae, duodenal hernia, duodenal obstructions caused by annular pancreas, duodenal ulcer, etc.

The chapter on x-ray diagnosis has been written by A. Judson Quimby, and that on Duodenal Parasites by Bailey K. Ashford. The latter is admirable.

As a reference book on the incidence, details and statistics of all types of duodenal abnormalities this volume is heartily recommended.

L. M.

An Introduction to Dermatology. By RICHARD L. SUTTON, SR. and RICHARD L. SUTTON, JR. Illust. 565 pp. $5.00. (*C. V. Mosby Co., St. Louis, 1932.*)

"This book is intended primarily for students." It is essentially an abridged edition of the senior author's more massive textbook. It is easily read, well illustrated, humanely simplified. For students it should be a great boon in all save one quality; namely, that it will leave them with the vaguest and most empirical ideas on therapy. In subsequent editions it is felt that a chapter on this matter would meet with popular acclaim.

W. J. T.

Nursing in Nervous Diseases. By JAMES W. MCCONNELL. 1932. 153 pp. $1.50. (*F. A. Davis Co., Phila., Pa.*)

Poorly arranged and uninteresting in appearance. Very little, if any, emphasis is given to important points. Conveys valuable information, but this is very hard to find. Might be used for supplementary reading.

M. B. D.

Manual of Public Health Nursing. Prepared by The National Organization for Public Health Nursing. 1932. 2nd edition. 253 pp. $1.50. (*Macmillan Co., New York.*)

General plan and content same as in first edition, with some changes to bring the text up to date.

M. B. D.

The Social & Ethical Significance of Nursing. By ANNIE WARBURTON GOODRICH. A Series of Addresses. $3.00. 401 pp. (*The Macmillan Co., New York.*)

This group of addresses is valuable for its informative and historical content. Should be available for all nurses.

M. B. D.

The Story of Medicine. By VICTOR ROBINSON. 1931. 527 pp. $5.00. (*Albert & Charles Boni, New York.*)

There are many ways of writing history and when that history is a history of the writer's own profession, the way in which he writes it is usually more or less evidently correlated to the type of his own professional life. Dr. Robinson has been distinctly a writer rather than a physician. He is not the type of active practitioner who snatches from his work an hour or two a day to put together an

article on Hippocrates or Vesalius. Dr. Robinson always writes vividly. His writing is surcharged with the reactions of his own personality to events. His is not the impersonal, objective attitude of the professional historian, who never allows his emotions to tinge the atmosphere of his historical work. This is refreshing and human. It gives to his book a certain vividness and humanness which is often lacking in historical writing. Here these personal reactions are merely incidental to sound and interesting historical discussion and analysis. Every modern medical historican is indebted more or less to Professor Sudhoff and it is not difficult to trace in the present work the influence of the greatest modern figure in the field of medical history.

J. R. O.

Human Values in Psychological Medicine. By C. P. BLACKNER. 179 pp. $2.25. (*Oxford University Press, New York, 1933.*)

This book can not possibly be read by any one who is liable to be interrupted every few minutes by medical or social obligations. Its reading requires concentration and clear hard thinking. Dr. Blackner's endeavor is to formulate some Freudian concepts which have never been adequately expressed. The main aim in the book, however, is given in the preface, *viz.*, that "the science of medical psychology would be further advanced if attention were turned to the personal characteristics and idiosyncracies of individual sufferers." The secondary aim of the author is defined as an attempt to relate to the principles of biology the principles of psychological medicine. Perhaps the most valuable and interesting portion is chapter VII, which deals with the aesthetic and pivotal values of mental patients.

J. R. O.

Psychology in General Nursing. By ISABEL WILSON. 216 pp. (*London, Edw. Arnold & Co., 1931.*)

An interesting, concise and helpful treatise on psychological mechanisms, which might well be included in the reading list of all nurses.

M. B. D.

The American Illustrated Medical Dictionary. By W. A. NEWMAN DORLAND. 1493 pp. [16th edition.] Revised and enlarged. $7.50. (*W. B. Saunders Co., Phila., 1932.*)

Many new and useful features have been added in this [16th] edition. Unquestionably one of the finest sources for medical reference published to date.

G. B.

Clinical Disorders of the Heart Beat. By THOMAS LEWIS. 7th Edition. (*Shaw & Sons, Ltd., Fetter Lane, London, 1933.*)

A new edition of what, in the reviewer's opinion, is by far the best of Sir Thomas's seven published books.

A. G.